INTERNATIONAL MEDICAL DIGEST

"A Monthly Abstract Journal of Current Literature"

Edited by ROBERT A. STRONG, M. D.
with the collaboration of
FREDERICK TICE, M. D.
IRVINE McQUARRIE, M. D.
MAXWELL M. WINTROBE, M. D.

DEC 4 1950

Volume 57 NOVEMBER, 1950 Number 5

CONTENTS

GENERAL MEDICINE

Response to Adrenocorticotropic Hormone and Cortisone in Persons with Carcinoma, Leukaemia, and Lymphosarcoma—*Tom D. Spies, Robert E. Stone, Guillermo Garcia Lopez, Fernando Milanes, Ruben Lopez Toca and Alfredo Reboredo* 259

An Evaluation of Reported Poisonings by Acetylsalicylic Acid—*Leon A. Greenberg*. 262

The Treatment of Angina Pectoris with a Preparation of Khellin (*Ammi Visnaga*)—*Charles A. Armbrust, Jr. and Samuel A. Levine* 265

Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests—*Maurice M. Best and Walter S. Coe* 266

Synthetic and Fermentation Type Chloramphenicol (Chloromycetin) in Typhoid Fever. Prevention of Relapses by Adequate Treatment—*Joseph E. Smadel, Charles A. Bailey and Raymond Lewthwaite* 268

A New Mercurial Diuretic—*A. Ravina*..... 272

Comparison of Mercurial Diuretics and Routes of Administration with Special Reference to Thiomerin—*William J. Atkinson, Jr. and Leo V. Mulligan*..... 274

Dimercaprol in Acute Lead Poisoning—*Poul Bastrup-Madsen* 275

Effective Control of an Outbreak of Rabies in Memphis and Shelby County, Tennessee—*Ernest S. Tierkel, Lloyd M. Graves, H. G. Tuggle and Samuel L. Wadley* 276

Infection of Laboratory Workers with Coxsackie Viruses—*Ernest W. Shaw, Joseph L. Melnick and Edward C. Curnen* 279

The Bornholm Disease and the Viruses of Coxsackie—*A. Plichet* 281

Primary Carcinoma of the Lung—*Evarts A. Graham* 283

The Effect of Streptomycin on Tuberculous Meningitis—*Henry D. Brainerd and Henry R. Eagle* 285

PEDIATRICS

Aerosol Streptomycin Treatment of Advanced Pulmonary Tuberculosis in Children—*Joseph B. Miller, Harold A. Abramson and Bret Ratner* 288

A Comparison of "Symptomatic Treatment," Gamma Globulin, and Penicillin in the Treatment of Scarlet Fever—*Louis Weinstein and Samuel F. Potsubay* 293

Congenital Malaria. Report of 3 Cases—*B. S. Jones* 296

Erythroblastosis Fetalis. Problems in the Interpretation of Changing Mortality in Erythroblastosis Fetalis — *Victor C. Vaughan, III, Fred H. Allen, Jr. and Louis K. Diamond* 298

The Treatment of Whooping Cough with Nebulizations of Streptomycin—*Mario Seraphico* 301

A Note on the Treatment of Diaper Rash with Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Roccal)—*William Pfeffer, Jr. and Clement A. Smith* 302

Poliomyelitis and Immunization Against Whooping Cough and Diphtheria—*H. Stanley Banks and A. J. Beale*..... 304

SYMPOSIUM SECTION

Khellin in Coronary Inadequacy 306

EDITORIALS

Irradiated Plasma-Borne Hepatitis 309

Congenital Malaria 310

W. F. PRIOR COMPANY, INC. • *Publishers* • HAGERSTOWN, MARYLAND

Entered as Second-Class Matter, June 17, 1920, at the Post Office at Hagerstown, Md., under the Act of March 3, 1879.

Copyright, 1950 by W. F. Prior Company, Inc.

$3.00 Annually in U. S. A.

Printed in the United States of America

THE INDEX of this number includes July, August, September, October and November.

International Medical Digest

Volume 57 NOVEMBER, 1950 Number 5

General Medicine

Response to Adrenocorticotropic Hormone and Cortisone in Persons with Carcinoma, Leukaemia, and Lymphosarcoma — SPIES, TOM D., STONE, ROBERT E., GARCIA LOPEZ, GUILLERMO, MILANES, FERNANDO, LOPEZ TOCA, RUBEN AND REBOREDO, ALFREDO — *Lancet*, 2: 241 (August 12) 1950.

The patients in this study were selected after careful histopathological examinations. "Of the 3 patients with carcinoma 2 had had surgical procedures and x-ray therapy and could not be benefited further, while the third had refused to have the carcinoma of his lip excised. All had excruciating pain and were incapacitated. Final criteria were that the primary site of the lesion must be visible to the unaided eye, that the patients must be cooperative, and that they should agree to have biopsies made whenever necessary. The 5 patients with leukaemia were selected arbitrarily after determining that they had acute leukaemia and that they had to have at least three blood transfusions weekly; four of them had lymphatic leukaemia and 1 had myelogenous leukaemia." The 2 patients with lymphosarcoma were selected because they had great pain, were unable to work, and wanted to cooperate in the studies.

"Carcinoma.—Of the patients with carcinoma 2 were treated with synthetic cortisone acetate and 1 with pituitary ACTH. In the 2 patients who received cortisone the condition was worse, and the improvement less, than in the patient given ACTH. In both of them the involved tissues of the tongue, mouth, and regional lymph nodes were matted into a hard firm mass which protruded several centimetres. Each patient was given a total of 3 Gm. of cortisone in divided doses of 150 mg. daily intramuscularly. Following this therapy they had a striking increase in sense of well-being and appetite: The amount of narcotics used could be reduced to about one tenth of what was previously necessary, and the patients became interested in carrying on a normal life. But histological examination showed no change in the neoplasms which were composed of large anaplastic epithelial cells of squamous type, with hyperchromatic nuclei, numerous mitotic figures, and involvement of the stroma. Despite the large amount of cortisone administered, neither patient developed any evidence of water or salt retention; and when the injections were discontinued there was no diuresis or loss of body weight.

"The following is an account of the response of the patient given ACTH."

"A white man, aged 60, complained of swelling and pain of the right side of the lower lip. It had begun nine months previously and had grown progressively worse, but he had refused operation. The lesion, which was hard and sensitive, was a large ulcerated area covered with greyish white exudate; the crater was about 1 cm. across and its edge was slightly elevated. The entire area of involvement was rounded and about the size of a walnut. He was unable to spit and he drooled continuously. His false teeth had been broken for five years, and the break was exactly opposite the central portion of the crater of the tumour. (To evaluate the effectiveness of therapy, the dentures were not changed during the studies.) The lymph glands on the right side of the neck were firm and enlarged, the largest being about 1 cm. long; they were not tender. The tongue and buccal mucosa membrane appeared normal.

"A biopsy specimen was described as follows: 'Tumour masses growing in cords and strands almost completely replace the dermal surfaces. These tumour masses tend to keratinise at their centres. There is marked inflammatory infiltration around the tumour strands. Diagnosis: squamous

cell carcinoma of the lip, grade II.' The blood levels were within normal range. The pulse, temperature, and respiration were normal, and the blood pressure ranged from 122/80 to 130/80 mm. Hg.

"The patient was given a total of 270 mg. of ACTH in five days, administered in 15 mg. doses six hourly. Twelve hours after the first injection the size of the lesion had noticeably decreased and it was considerably less sensitive. He volunteered that he had more energy than for several months and for the first time in many weeks had a desire for food. Next day the lesion was still smaller and there was less exudate from the crater. It was not painful and he could move his lip with ease and without pain though it was still sensitive to touch. Therapy was discontinued after five days because no more ACTH was available. During therapy the blood pressure increased slightly, ranging from 144/74 to 150/82; after therapy was discontinued, it returned to the initial level. The blood values remained within normal range.

"The report on a second biopsy specimen was: 'Section through the specimen shows a thin margin of relatively normal-appearing squamous epithelium. In the central portion there is an interruption with downgrowth of broad sheets of squamous epithelium. These show some variation in nuclear size; occasional mitotic figures. In an occasional area there is keratohyalin production with formation of small pearls. Around the invading squamous epithelial cells there is some chronic inflammation. Diagnosis: squamous cell carcinoma, grade II.'

"Four months after ACTH therapy was discontinued the lesion measured 12 by 7 mm. Though still sensitive to touch, it was not painful otherwise. At this time he was given a second series of injections of ACTH until he had received 576 mg. during 24 days, administered intramuscularly in 8 mg. doses eight hourly. On the second day there was a suggestion of less thickness of the lesion. Gradually it became smaller and less firm. By the eleventh day the patient was certain that the lesion was only half the size it had been at the beginning of treatment and he said that his lip felt normal; the ulcerated area had decreased to the size of a pinhead. By the twentieth day all pain and soreness had disappeared. At this time he went back to work for the first time in over a year. On the sixteenth day of therapy he had developed slight oedema of the feet and ankles which disappeared the following day. The blood pressure before therapy ranged from 108/70 to 118/74, and during therapy from 136/70 to 136/76; after the ACTH was discontinued, it returned to the initial level. The blood levels, temperature, and pulse and respiration rates remained normal throughout.

"The biopsy report after treatment was: 'Section through the specimen shows a margin of normal-appearing squamous epithelium. This is interrupted along one edge by the downgrowth of masses of squamous epithelium. These are very adult, are producing keratohyalin, and forming pearls. They extend down to the lower margin of the biopsy specimen. There is some acute and chronic inflammation associated with the lesion. Diagnosis: squamous cell carcinoma of the lip, grade II; acute and chronic inflammation.'

"Though ACTH therapy was discontinued six months ago, the patient insists, and correctly, that the lesion is still decreasing in size. He has been advised repeatedly to have it excised, but so far he has refused to do so.

"Leukaemia.—The results of administration of pituitary ACTH to the 5 patients with leukaemia were extremely variable." One patient died on the fourth day without being benefited in any way which could be determined. "The patient with the myelogenous leukaemia had a great clinical and moderate haematological response but developed hallucinations after 2,500 mg. of ACTH had been given in 25 days. By that time her bone marrow, which before therapy had been almost entirely replaced by leukaemic cells, was about one-half erythroid element and one-half leukaemic. When she developed hallucinations, treatment was discontinued and they disappeared within 24 hours. ACTH therapy was resumed after a three day interval at the same dosage level of 25 mg. four times a day, and hallucinations reappeared within 48 hours. From that time on, it was impossible to give her 100 mg. of ACTH in 24 hours without the recurrence of hallucinations. Hence it was a losing

fight and she died within the third month of her illness. The red blood cells and haemoglobin increased somewhat till the time of her death.

"The other 3 patients with leukaemia are living. One of them, under observation for a year, has had two series of ACTH injections, each lasting 14 days at a dosage level of 100 mg. in 24 hours. No untoward symptoms developed; the enlarged lymph nodes in the neck and axillas decreased in size, and the bone marrow became much more normal in appearance though it still contained some abnormal cells. Five months after the first period of ACTH therapy the symptoms recurred and she was treated again with similar results. Now, six months after the last series of injections, another relapse seems imminent. The fourth patient had rheumatoid arthritis as well as leukaemia and was given 40 mg. of ACTH four times a day for 10 days. Within three days of the first injection the symptoms of arthritis decreased and the bone marrow appeared somewhat more normal. His reticulocytes rose rapidly during the next week, and the red cell count and the haemoglobin content of the blood increased to within normal limits within three weeks, whereas before treatment it had been necessary to give him three transfusions a week. At the present time, transfusions are unnecessary." The authors see him frequently, for they suspect that he will relapse rather promptly because of the many abnormal young cells in the peripheral blood and in the bone marrow.

"The fifth case requires a more detailed report":

"A boy, aged 7 years, was admitted to the hospital with acute leukaemia. He had suddenly become ill three weeks previously; acute lymphatic leukaemia had been diagnosed; and he had had three or four transfusions weekly. When admitted, he was bleeding profusely from nose and gums and was semicomatose, refusing food and water when aroused.

"The initial peripheral blood findings in the hospital were: red blood cells 2.55 million; white blood cells 6,350; haemoglobin 8.4 Gm. per 100 ml. (54 per cent); and reticulocytes 0.6 per cent. In a study of the blood smear 23 per cent of the white cells were identified as belonging to the polymorphonuclear leucocyte series and 54 per cent as belonging to the lymphoid series; the remaining cells were so immature that they could not be classified. The blood platelet count was 50,820. The sedimentation rate, with correction, was 64 mm. per hour. Sternal punctures were made repeatedly and marrow was obtained with difficulty each time. Microscopic examination showed no areas of normal bone marrow and many areas characterised by clusters of white cells of various ages, sizes, and shapes. Nearly all were immature; some were recognised as being of the lymphoblastic series. A few tiny areas of erythroid elements were seen.

"As soon as the base line observations were completed, the patient was given ACTH intramuscularly, in sterile physiological solution of sodium chloride, in doses of 10 mg. every six hours. This therapy was continued each day for 15 days, during which time he had no transfusions. On the third day the bleeding ceased, and the reticulocyte count was 6.4 per cent. The reticulocytes peaked at 18 per cent on the eighth day, and at the end of the 15 days the blood counts were: red cells 3.38 million; white cells 5,350; haemoglobin 8.9 Gm. (59 per cent); and reticulocytes 5.0 per cent. A smear of the peripheral blood showed, polymorphonuclear leucocytes 74 per cent, lymphocytes 25 per cent, and one unclassified cell. The platelet count was 122,000. Sternal puncture showed a striking change in the bone marrow; many normal areas of blood regeneration were apparent though clusters of abnormal white cell proliferation (leukaemia) were also found. The sedimentation rate, with correction, was 15 mm. per hour. The temperature, which had been 38.2° C. on admission, fell to 36° C. on the second day of therapy and did not rise above 36.4° C. while he was receiving the injections. The pulse rate, which was 80 at the beginning of therapy, ranged between 128 and 140 throughout therapy. The average respiration rate was 18 before, during, and after therapy. Before therapy the blood pressure was 90/50; by the eleventh day it had increased to 120/60; and on the fourteenth day it was 130/60. His body weight, which was 36 pounds at the beginning of therapy, increased to 40½ pounds, but he did not develop any

clinical oedema and had no diuresis after the ACTH was discontinued. On the second day of therapy he got out of bed, played around the ward, and was interested in everything going on. From that day he ate all the food on his trays, improved steadily in strength and vigour, and was as active as a normal child.

"Twenty-four hours after the injections of ACTH were discontinued he was weak, bleeding, crying, and obviously relapsing. Next day a smear of the peripheral blood showed: polymorphonuclear leucocytes 28 per cent, band cells 1 per cent, eosinophils 1 per cent, lymphocytes 65 per cent, myelocytes 1 per cent, and lymphoblasts 4 per cent. After 48 hours without injections of ACTH he was started on 80 mg. intramuscularly in doses of 20 mg. every six hours. On the second day there was a striking clinical improvement. He began eating well and playing again. On the ninth day all the examining physicians concurred that he now had a so-called 'moon-face.' By this time his body weight was 6 pounds greater than at the beginning of therapy but he had no pitting oedema of the ankles. His condition was such that the only hope was to continue the ACTH injections, so a daily dosage level of 80 mg. was continued for 10 days. Then it was reduced to the following total amounts daily, injected in divided amounts every six hours: 40 mg. for one day; 30 mg. for five days; 20 mg. for one day; 15 mg. for three days; and 12 mg. for eight days. Before the reduction in dose the blood counts were: red cells 5.12 million; white cells 9,300; haemoglobin 13.2 Gm. (86 per cent); and reticulocytes 0.4 per cent. A smear of the peripheral blood showed: polymorphonuclear leucocytes 71 per cent, band cells 4 per cent, basophils 1 per cent, eosinophils 3 per cent, and lymphocytes 21 per cent. The platelet count was 656,700. The sedimentation rate with correction was 5 mm. per hour. The bone marrow showed a striking change toward normal but there were some abnormal collections of white cell elements.

"ACTH injections were discontinued after he had a total of 1,750 mg. in 43 days. By this time the moon-face was more pronounced and his body weight, which was 36 pounds before therapy, had increased to 45 pounds. At this time he developed some acne limited to a small area on the chin. In the four weeks that elapsed after ACTH therapy was discontinued the red cell count, white cell count, and haemoglobin remained essentially unchanged. The day after therapy was discontinued the differential count showed: polymorphonuclear leucocytes 31 per cent, metamyelocytes 1 per cent, basophils 1 per cent, and lymphocytes 67 per cent. In the next four weeks the sedimentation rate, with correction, varied between 30 and 51 mm. per hour. The moon-face and the acne persisted; his body weight increased to 50 pounds (no evidence of water or sodium retention). He felt well and had a good appetite until the twenty-ninth day after therapy was discontinued. Then he suddenly relapsed. His temperature was 39.5° C.; his pulse and respiration rates were rapid. Many immature cells were in his peripheral blood and he began bleeding from the gum margins. At the time of relapse the blood counts were: red cells 4.64 million; white cells 19,500; haemoglobin 12.4 Gm. (81 per cent); and reticulocytes 0.2 per cent. A differential count showed: polymorphonuclear leucocytes 20 per cent, metamyelocytes 4 per cent, band cells 8 per cent, and lymphocytes 68 per cent. The sedimentation rate corrected was 52 mm. per hour.

"ACTH in divided doses was started again. At the present time, after nine days of therapy, his response is similar to that seen in the two previous periods of therapy.

"Lymphosarcoma.—The 2 patients with lymphosarcoma responded promptly and similarly to synthetic cortisone acetate. Both had a great gain in strength, and a desire to eat and to work, and in both the symptoms disappeared. One remained essentially free of symptoms for about three weeks and the other for about six weeks before the relapse occurred."

An Evaluation of Reported Poisonings by Acetylsalicylic Acid — GREENBERG, LEON A. — *New England Journal of Medicine*, 243: 124 (July 27) 1950.

"Acetylsalicylic acid, like most drugs that are useful in therapeutic doses, causes toxic symptoms if sufficiently large amounts are taken; the severity of the symptoms increases as the dosage is further

increased. The symptoms vary from mild nausea, vertigo or tinnitus to serious collapse, unconsciousness, coma or death. In a review of hospital records the following symptoms of acetylsalicylic acid toxicosis were observed: dizziness, tinnitus, deafness, nausea, vomiting, fever, prostration, rapid pulse, profuse perspiration and in severe cases sometimes accompanied by subnormal temperature, restlessness and coma. In severe cases there was also a decrease in the alkali reserve of the blood, presence of albumin, casts and red blood cells in the urine, and frequently acetone in the urine.

"Besides the general toxic effects of acetylsalicylic acid, idiosyncrasy to the drug has been observed in some allergic persons. In these cases the symptoms are evoked by small amounts and consists of typical allergic manifestations such as skin eruptions, edema, asthma, vasomotor disturbances, headache, perspiration, salivation, palpitation, syncope and collapse. Idiosyncrasy, however, is relatively infrequent."

"The effects of acetylsalicylic acid on individual organs and functions of the body have been investigated extensively. In the study of these effects on the cardiovascular system, perfusion of the isolated heart has often been employed. Only extremely high concentrations of the neutralized acid, far in excess of those found in vivo, were observed to depress cardiac action. The erroneous concept that acetylsalicylate has an intensely toxic action on the isolated heart, even in concentrations occurring in the blood of persons taking small therapeutic doses, arose from perfusion of the heart with modified Ringer's solution from which sodium bicarbonate was omitted, thus preventing the neutralization of the acetylsalicylic acid. In the absence of a neutralizing base in the perfusing fluid the toxic effects observed were due to the acidity and not to the salicylate. Only a neutral salt of acetylsalicylic acid can exist in the blood in vivo."

"Therapeutic doses have no effect on cardiac action in man.

"No significant effects of small amounts of acetylsalicylic acid on respiration or on the acid-base equilibrium of the blood have ever been reported. Marked consequences of large amounts have often been observed in animal experiments and in man. These have consisted of alterations in the volume of breathing, changes in the carbon dioxide content and the alkali reserve of the blood, changes in the *p*H of the blood and in the acidity of the urine and alterations in the urinary excretion of ammonia and urea."

"It may be concluded from the literature that large amounts of acetylsalicylic acid frequently cause gastrointestinal disturbances; small therapeutic doses rarely do so, and only in sensitive persons.

"There is no indication that small therapeutic doses have any effect on the kidneys or on renal function."

"Tinnitus and slight deafness are common symptoms of salicylism. In the treatment of rheumatic fever, prior to the routine clinical use of blood analysis to determine the concentration of salicylate present, the optimum rate of administration of salicylates was often judged by the appearance of these symptoms. There is only meager evidence, however, that small doses, as used for analgesia, affect the auditory function, and there is no evidence that such amounts are injurious to the ear even when taken repeatedly.

"A possible relation between intensive salicylate medication and bleeding has been repeatedly suggested in the literature. In the past few years many investigators have reported a prothrombinopenic effect of salicylate in man. In most of these reports the doses were high, and the administrations of large therapeutic doses of acetylsalicylic acid and repeated administration of small amounts were not found to have a prothrombinopenic effect. There is little doubt, from present knowledge, that salicylate in sufficiently large dosage has a prothrombinopenic action in man, and that hypoprothrombinemia is associated with a prolonged bleeding and clotting time. This effect may be a contributing factor in the hemorrhages observed in diseases for which salicylate has been given in large and repeated doses. The prothrombinopenic effect, however, is limited to large doses, repeatedly administered over a prolonged period, and there is no evidence that small doses as used for analgesia cause any clinically significant hypoprothrombinemia."

"Only 88 cases of poisoning by acetylsalicylic acid have been reported from which such data as the dosage, duration

of administration, severity of symptoms and reason for taking the drug may be obtained."

The reasons for taking acetylsalicylic acid in these 88 cases were as follows: rheumatic fever, 16 cases; analgesia, 17 cases; other medicinal use, 10 cases; accidents, 5 cases; suicidal attempts, 24 cases; not stated, 16 cases.

Doses of acetylsalicylic acid taken were as follows: up to 1.5 Gm., 14 cases; 1.5 to 12 Gm., 19 cases; over 12 Gm., 38 cases; not stated, 17 cases.

Period over which acetylsalicylic acid was taken was as follows: single dose, 16 cases; 1 day, 22 cases; up to 1 week, 12 cases; over 1 week up to 1 month, 3 cases; over 1 month up to 1 year, 2 cases; more than 1 year, 4 cases; duration unknown, 3 cases.

Severity of intoxication was as follows: slight, 18 cases; moderate, 22 cases; severe, 17 cases; fatal, 31 cases.

"Few cases of fatal poisoning have occurred in which the administration was reliably observed by a physician and the exact dose known. In most cases the dose was approximated by circumstantial evidence such as an empty bottle thought to have contained some amount of the drug or, more often, the word of the family that the victim took a certain number of tablets during the day. Such evidence has little quantitative validity.

"Another point of uncertainty concerning the lethal dose of acetylsalicylic acid lies in the designation of the cause of death as due to this drug. In many cases, as when a person is acutely ill and dies after a seemingly small dose of the drug, the decision whether the acetylsalicylic acid was the main or a contributing cause or of no effect is wholly a matter of opinion."

"The records of the United States Bureau of the Census provide statistics on deaths reported as due to acetylsalicylic acid in the years 1926, 1928 and 1930 through 1943. Since 1933 the death registration system of the Bureau has included the 48 states. . . . The number of deaths and the rate per 1,000,000 population are low and show no trend over the entire period. During the period 1939 through 1943 in the United States the average annual total mortality from accidental poisoning by all solids and liquids was reported as 1,267, of which about 1 per cent was attributed to acetylsalicylic acid. This low incidence is striking in view of the extensive use and wide availability of the drug.

"Besides being relatively few in number, the deaths attributed to acetylsalicylic acid in the statistics of the Census Bureau undoubtedly include many in which a fatal disease or other cause of death was present, so as to render the toxic symptoms of the drug only incidental. In such cases, even if the certifying physician reports an acute or chronic disease or some other factor as the primary cause of death, acetylsalicylic acid poisoning will nevertheless always be recorded as the primary cause in the official statistics."

In a series of 31 cases, 11 were cases of suicide in which quantities of the drug ranging from 20 to 75 Gm. were taken at one time.

"In 6 fatal cases, not reported as suicides, large to massive amounts of acetylsalicylic acid were known to have been taken. Two of these persons had histories of mental disease. Another took 50 Gm. of the drug, supposedly for a toothache. Still another, acutely ill with influenza, found access to, and consumed, 60 Gm. of acetylsalicylic acid.

"In 9 cases of death attributed to acetylsalicylic acid the amounts of drug taken were not known. In 2 of these the contents of the viscera indicated that large amounts of salicylate had been consumed. Two of these persons had histories of mental illness. In 2 cases a serious underlying disease was present, in 1 there was an unspecified ailment and in 1 other drugs were taken simultaneously.

"Besides these 31 nonallergic deaths attributed to acetylsalicylic acid, 7 deaths have been reported as being due to idiosyncrasy to the drug. In these cases typical allergic manifestations were observed, and death resulted from small doses of the drug. All the victims were asthmatic and had shown hypersensitivity to acetylsalicylic acid on one or more previous occasions.

"This review of the reported cases of death attributed to acetylsalicylic acid reveals several noteworthy features aside from the small number of cases. A large portion of them were suicides. These, as well as another large portion that were not

suicides, consumed amounts of acetylsalicylic acid far in excess of the doses used therapeutically. In the other cases the amounts were unknown but, from the symptoms observed, can be presumed to have been large. In several cases of poisoning there was a history of mental disorder; in many others there were severe underlying diseases. Severe poisoning, or death from large or massive doses of any drug, whatever the reason for its consumption, is not a criterion of the possible danger in its therapeutic use. Finally, there is a conspicuous absence of reports of serious poisoning or death, other than allergic poisonings, associated with ordinary therapeutic use of acetylsalicylic acid, even when this use has been continued over a long period."

The Treatment of Angina Pectoris with a Preparation of Khellin (Ammi Visnaga) — ARMBRUST, CHARLES A., JR. AND LEVINE, SAMUEL A. — *American Journal of the Medical Sciences*, 220: 127 (August) 1950.

"Fifty-three patients with a classical history of angina pectoris were studied. The patients were divided into 2 groups." Group 1 consisted of 28 patients of which there were 17 males and 11 females, varying in age from 44 to 77 years with an average age of 60 years. "The duration of the angina pectoris varied from 2 months to 16 years, and was greater than 2 years in 16 patients. Seven patients had what was regarded as mild angina pectoris (7 or fewer episodes of pain per week), 17 moderately severe (up to 30 episodes of pain per week with occasional attacks at rest), and 4 patients had severe angina pectoris (as many as 150 episodes per week with numerous spells at rest). . . . All patients received a routine physical examination. Roentgenograms of the chest and electrocardiograms consisting of the 3 standard limb leads, 3 augmented unipolar limb leads and 6 precordial leads. Eight patients had normal electrocardiograms, 13 showed the pattern of left ventricular hypertrophy (3 of these in addition had evidence of an old myocardial infarction), 1 showed incomplete right bundle branch block, and 2 had left bundle branch block. Nineteen patients had an exercise tolerance test as described by Master before therapy was started. Thirteen of these tests were taken as positive; i.e., electrocardiographic changes were present. . . . Twenty-four patients were observed for periods of from 1 to 8 months. Four were studied for 3 weeks or less because of their refusal to continue treatment. During the time of observation the patients were maintained alternately on periods of khellin medication and of placebo medication, each from 3 to 10 weeks in duration. Neither the individual under study nor the observers knew whether the preparation being used was placebo or khellin. Early in the study the placebos and the drug were not identical in appearance but at some time during the subsequent observations all patients received placebos identical to khellin in all appearances. The patients were seen at intervals of 1 to 3 weeks during the entire period of observation."

Group 2 consisted of 25 cases treated in the office practice of one of the writers for periods of 7 days to 2 weeks. "There were 19 males and 6 females, varying in age from 44 to 76 years, with an average age of 57 years. The duration of the angina pectoris varied from 1 to 14 years. No exercise tolerance tests were performed and no placebos were used.

"Each patient of both groups kept a written record of the number of nitroglycerin tablets used and the number of anginal attacks per week while under observation. They were encouraged to carry on their ordinary activities. Khellin was administered by mouth to each patient, (in the form of 'Eskel' tablets, 40 mg. t.i.d.) after meals or with meals. In some patients the dose was increased to 4 times daily or decreased to once or twice daily depending on whether or not side effects developed."

"Khellin was judged to be of definite value when the number of episodes of angina pectoris or the number of nitroglycerin tablets used per week was 50 per cent or less than when on placebo therapy, of slight value when the number was only slightly less than when on placebo treatment, and of no value when the placebo effect was equal to or better than the drug results. . . . Improvement was noted in 16

of 28 patients in group 1. In 3 cases in which the drug was judged to be of no value, the trial was 3 weeks or less in each. It was discontinued because of side effects. Six patients who, before therapy, had positive electrocardiographic changes on exercise had this test repeated after a course of treatment. In 4 the same electrocardiographic changes took place on exercise but the pain that they had previously experienced did not develop. The other 2, who had no pain on the exercise test, had the same electrocardiographic changes before and after treatment.

"The patients' opinion as to the value of the drug was also analyzed. Nineteen of the 28 patients said that the drug was helpful. They stated that they were having fewer episodes of pain, and, more particularly, that when the pain did occur it was of a milder nature. The ability to walk greater distances than prior to treatment was mentioned by many; i.e., their exercise tolerance was increased. There were only 3 cases of the 19 who said they were better who did just as well on placebos. In the other 16 cases the subjective improvement which the patient ascribed to the khellin disappeared when placebo therapy was again instituted.

"Thirteen of group 2 patients stated that the drug was helpful in that they had less pain, used fewer nitroglycerin tablets and could walk longer distances.

"When factors such as age, sex, hypertension and duration of angina were considered for both groups, there was nothing to suggest that any particular type of patient responded any better than another."

"Nineteen of the patients in group 1 complained of untoward effects. The most common and troublesome of these were anorexia, nausea and dizziness. In many patients the nausea and loss of appetite was not distressing enough for them to discontinue the drug completely but was bothersome, and some took the drug irregularly. Nausea occurred in 18 of the 28 cases, anorexia in 15 cases and dizziness in 10 cases. In 5 patients the symptoms were so severe that they refused any further therapy. In several, dizziness was so serious that they were unable to continue their activities and had to remain in bed, 2 refusing further treatment. Insomnia developed in several but was severe in only 1 case. Two patients developed a maculopapular rash. The rash required approximately 3 weeks to disappear and reappeared when the drug was administered again. All of these side effects developed on dosages of 120 mg. daily. Twenty-one patients were able to continue the drug if the dosage was lowered to 40 or 80 mg. per day or continued in spite of the side effects. Seven were unable to take the drug at any level of dosage.

"Fourteen in group 2 of the 25 patients complained of nausea, anorexia and dizziness. The development of these untoward side effects did not seem to influence the response of the patient to the drug, except where the drug had to be discontinued."

Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests—BEST, MAURICE M. AND COE, WALTER S. — *Circulation*, 2: 344 (September) 1950.

"The 9 patients selected for this study fulfilled the following criteria: history of classic angina pectoris on exertion; no evidence of congestive heart failure, hyperthyroidism or anemia; no recent myocardial infarction; and at least 1 of 3 electrocardiographic tests for coronary insufficiency positive."

"All patients were observed through at least a one month control period. They then received khellin, 50 mg. (one tablet) orally three times a day for a period ranging from two to four weeks. All patients received one placebo tablet three times a day for at least one month. Four patients received these tablets before, and 5 at the completion of khellin therapy. The placebo tablets were identical in appearance and indistinguishable in taste from the khellin tablets. Daily nitroglycerin consumption was recorded throughout each period. The observer who recorded symptomatic response and nitroglycerin consumption was unaware which type of tablet the patient was receiving. All patients remained ambulatory and continued their usual activities throughout the periods of study."

"The following tests were done before treatment, at completion of khellin therapy, and following placebo administration:

"1. Exercise tolerance test, as described by Master and associates with graded exercise on standard steps. The patients rested 15 minutes and then performed the standard amount of exercise as indicated by tables based on sex, age and weight, and completed the determined exercise in one and one-half minutes. Electrocardiograms consisting of leads I, II, III, and V_4 were recorded before exertion. These were repeated immediately on cessation of exercise and at intervals of 3, 5, and 8 minutes thereafter. In the event of pain, an immediate electrocardiogram was recorded and nitroglycerin, 0.43 mg. was given.

"Criteria for a positive test consisted of a depression of the RS-T junction of at least 1 mm. in any lead, conversion of an upright T wave to an isoelectric or inverted T in leads I, II, or V_4; or conversely the conversion of an inverted T wave to an upright T wave in these leads. The appearance of multifocal ventricular premature contractions was also considered an abnormal response.

"2. Anoxemia test was performed according to the method of Levy and his coworkers. A mixture of 10 per cent oxygen and 90 per cent nitrogen was administered through a gas machine equipped with a flutter valve so that no rebreathing occurred. Periodic analysis by the method of Haldane of the gas mixture revealed the oxygen content to remain constant at $10 \pm .02$ per cent. By means of a simple push button 100 per cent oxygen could be immediately substituted for the reduced oxygen mixture. A control electrocardiogram consisting of leads I, II, III, and V_4 was obtained initially. The oxygen-nitrogen mixture was then given for 20 minutes. Electrocardiograms were recorded at intervals of 5 minutes during the period of reduced oxygen administration and for 15 minutes thereafter. In the event of pain an immediate electrocardiogram was recorded and 100 per cent oxygen administered.

"Criteria for a positive test were similar to those of Levy: the sum of the RS-T deviations in all leads totals at least 3 mm., or a reversal in the direction of the T wave in leads I and V_4 if accompanied by RS-T depression of 1 mm. or more." The writers also considered the appearance of multifocal ventricular premature contractions to be an abnormal response.

"3. Ergonovine test was performed by the method of Stein. Each patient was required to rest at least 20 minutes and a control electrocardiogram consisting of leads I, II, III, and V_4 was recorded. Ergonovine maleate, 0.2 mg. was injected intravenously very slowly. The electrocardiogram was repeated immediately upon completion of the injection and at intervals of 3, 5, 15, and 30 minutes. Tablets of nitroglycerin, 0.43 mg., were given immediately if pain occurred.

"The criteria for a positive test were depression of the RS-T segment of 1 mm. in any lead or conversion of an upright to an isoelectric or inverted T wave in leads I, II, or V_4."

"Twenty-five tests were performed on the patients prior to treatment. Fourteen were positive. Ten of these 14 positive tests reverted to negative following khellin therapy. Two tests remained positive and two tests were not repeated. One patient developed chaotic heart action following ergonovine and another patient refused to permit the anoxemia test to be repeated. All tests reverted to their pretreatment status with placebo therapy."

"Precordial pain occurred during 17 of the 25 pretreatment tests. Pain occurred on 4 occasions during testing at the completion of khellin therapy. One patient experienced pain during the initial exercise tolerance test but had no pain on subsequent testing following khellin and placebo periods."

"Eight patients noted an increase in exercise tolerance and a decrease in number and severity of anginal attacks while under treatment with khellin as contrasted to the control period. . . . One patient reported symptomatic improvement with placebo tablets. The only patient in whom no subjective improvement occurred was thought to have syphilitic involvement of the coronary ostiums."

"Nausea and vomiting were the only toxic effects noted. These occurred in 3 patients but were not so severe as to limit the use of the drug."

"It would seem that khellin is of value in the treatment of angina pectoris."

Synthetic and Fermentation Type Chloramphenicol (Chloromycetin) in Typhoid Fever. Prevention of Relapses by Adequate Treatment — SMADEL, JOSEPH E., BAILEY, CHARLES A. AND LEWTHWAITE, RAYMOND — *Annals of Internal Medicine*, 33: 1 (July) 1950.

"The 23 patients with typhoid fever included in the present study were placed in one of three experimental groups. Eight persons in experiment 1 received the synthetic form of drug. Blood cultures from each of these were positive for *S. typhosa* prior to treatment. These 8 patients were divided into two equal subgroups, one of which was treated during the second week of disease and the other during the third to fifth week. In experiment 2 the group consisted of 12 patients each of whom had a positive culture of *S. typhosa* from blood, feces, or urine before treatment was begun. These were consecutive admissions representing unselected cases which were treated as soon after hospitalization as the diagnosis was established, varying from 8 to 67 days after onset of the disease. The members of this group were treated with either synthetic or fermentation type of drug. Experiment 3 consisted of 3 patients who were treated with fermentation chloramphenicol. . . . These, like the patients in the second experiment, represented the usual type of disease encountered in hospital practice in Malaya."

"The therapeutic regimen employed, irrespective of the type of chloramphenicol given, consisted of an initial oral dose of 3.0 to 4.0 Gm. of drug for adults followed by 3.0 Gm. daily until the temperature reached normal levels, after which 1.0 or 2.0 Gm. were given daily for a variable period of time."

Efficacy of Synthetic Chloramphenicol in Typhoid Fever.—"In general, the response of patients who received the synthetic drug was as satisfactory as would have been expected had the original fermentation type of antibiotic been employed. Furthermore, in the small subgroups of this experiment, treatment was apparently as effective when given during the third to the fifth week as it was when given earlier." The duration of fever after therapy was begun was approximately the same in members of the two groups with the exception of 1 patient whose 10 day febrile disease was prolonged by intestinal perforation. One patient, whose course was complicated by transient auricular fibrillation, was afebrile before and during the period of cardiac arrhythmia.

"Comparative Efficacy of Frequent and Infrequent Daily Doses of Chloramphenicol.—In the earlier studies on typhoid fever and in experiment 1, attempts were made to maintain a relatively constant and high blood level of chloramphenicol until the patient became afebrile, and a constant but somewhat lower level for a period of time thereafter. Accordingly, 0.25 Gm. doses of drug were given at intervals of two to three hours throughout the day and night during the early phase of illness and at four to six hour intervals in the later stages. Such a schedule was inconvenient, especially since nursing facilities were limited. In an attempt to simplify the procedure, a number of patients were given the same total daily dose which had previously been used but they received the drug in two divided doses at 12 hour intervals during the febrile period and in a single dose once daily after the temperature became normal. The results obtained in 8 of these patients showed that the simplified schedule gave as satisfactory results as had been obtained earlier."

"Following the oral administration of several grams of chloramphenicol to human beings, the drug appears in the blood within 30 minutes and its concentration rises progressively during the first two to four hours; it then remains stationary or falls slightly during the next few hours after which it diminishes progressively and becomes undetectable in 18 to 24 hours. . . . The levels fluctuated widely when relatively large doses of drug were administered to typhoid patients once or twice daily." The tabular data showed that on the 12 hour schedule appreciable amounts of drug; namely, 11 to 24 gamma per cc., were still present in the blood at the time the next dose was given. "In contrast, at the end of 24 hours there was little or no drug present in the blood of those who received a single daily dose. . . . The blood levels at six hours were somewhat higher in the patients on a twice daily

schedule than in those on a single daily dose."

Relation of Relapses to Duration of Treatment.—Early experience with chloramphenicol in the treatment of patients with typhoid fever indicated that relapses were more common in these patients than in those who ran the full course of the disease without benefit of specific therapy. "As observations accumulated, it appeared that the incidence of relapses was highest in that group which had received the smallest amount of drug over the shortest period of time. With this idea in mind, the duration of therapy was gradually prolonged." Forty-four patients with typhoid fever received chloramphenicol for varying periods of time. Two patients were omitted from consideration because they were first treated during a relapse of the disease. One patient is not included since he died during the course of the initial disease. "The total daily dose of drug given to each of the 44 patients, as calculated on the basis of body weight, did not vary appreciably at comparable periods during the first week of treatment."

The patients were divided into three groups. The patients included in groups A and B were those who were carefully selected and treated early in the course of their disease. "The composition of the two groups was relatively homogeneous and the patients differed mainly in the duration of their therapy. The majority of the persons included in group C were from the unselected series of typhoid patients who represented consecutive hospital admissions. On the average, treatment was started on the patients in groups A and B on the thirteenth day of illness and in group C on the twentieth day. The patients in group A received drug over a period of 4 to 8 days, those in B from 9 to 14 days and those in C from 14 to 19 days."

All relapses occurred in patients of group A who were treated for a period of 8 days or less. The clinical relapse began between 8 and 16 days, average 11, after therapy had been stopped, and it occurred between 26 and 44 days, average 32, after onset of disease. The development of recrudescent disease in 7 of these 13 patients in group A gives a relapse rate which is approximately four times that reported in typhoid patients who suffered the full course of the disease without benefit of specific therapy. "Since no relapses occurred in groups B and C, both regimens were equally effective in preventing relapses."

"Complications and Their Management. — Intestinal Hemorrhage: Intestinal hemorrhage was the most common complication encountered in the present group of 23 patients. It occurred in 5 persons between the twelfth and twenty-second day of disease which in 3 instances was before treatment was started. A member of this last group bled repeatedly before and after chloramphenicol was administered; he subsequently suffered intestinal perforation and died. Two others ceased bleeding before therapy was given and this complication did not recur." One patient had not yet become afebrile as a result of treatment when hemorrhage occurred while another patient had been free of fever for a day when bleeding developed. "Hemorrhage was of sufficient severity to induce shock in 3 of the patients." Blood transfusions given to 2 of these were apparently helpful but proved of little value to 1 patient who had additional complications.

"Intestinal Perforation: The records of the 2 patients who had intestinal perforation are of sufficient interest to discuss at some length."

A 13 year old Chinese male was hospitalized on the fifteenth day of a disease which was characterized by headache, cough, diarrhea and periods of delirium. "Rose spots, pulmonary rales, splenomegaly and mental confusion were noted on physical examination. Blood and feces, obtained before treatment was begun on the eighteenth day, yielded *S. typhosa* on culture; the urine gave negative results. The patient received the synthetic form of drug with an initial dose of 4.0 Gm. followed by 0.25 Gm. every two hours. The temperature came down by lysis on the second and third days of treatment and on the morning of the twenty-first day of illness, it approached normal. At noon the patient experienced a chill and his fever rose to 103.6° F. No obvious cause was found for these signs, and because the temperature promptly returned to normal, undue emphasis was not placed on the episode. However, later that day the patient com-

plained of generalized abdominal pain and refused to take the fluid diet which he had accepted previously. Physical examination at that time showed marked abdominal distention, and palpation revealed extensive muscular spasm of the abdominal wall and diffuse tenderness. Intestinal perforation was suspected. During the ensuing 24 hours, definite signs of pneumoperitoneum appeared and the amount of air apparently increased." Despite the white blood cell count of 2,100, it was the writers' opinion that the diagnosis of intestinal perforation with generalized peritonitis was warranted and that operative intervention was indicated. "Permission for the operation was not obtained until the following day and by then the patient seemed to be improving. Since under similar circumstances an earlier case of typhoid with intestinal perforation had been managed successfully on chemotherapy alone, and since the present patient was improving on a similar regimen, it was decided to avoid surgery. Throughout this episode and for the next few days the patient received 0.25 Gm. of chloramphenicol orally every two hours. In addition, at the time when surgical intervention had been decided upon, the patient was given intramuscularly a total of 650,000 units of penicillin and 3.0 Gm. of streptomycin, but these antibiotics were not administered subsequently. The physical signs which had led to the diagnosis of perforation and peritonitis disappeared over the next three or four days and on the tenth day of treatment the patient became permanently afebrile. He continued to receive 0.25 Gm. of drug every four hours for another three days after which chloramphenicol was discontinued. Although convalescence was uneventful, the patient was kept in the hospital for observation for another month. During this time repeated cultures of feces and urine were negative for *S. typhosa.*"

A 10 year old Chinese male was hospitalized on the eighth day of a febrile illness. "He had a mild fever of 99° to 101.0° F. with a pulse rate of approximately 120. The white blood cell count was 3,800 and the hemoglobin 9.0 Gm. per cent. A blood culture taken on the tenth day of illness was positive for *S. typhosa.* The low grade fever continued but the patient became increasingly toxic. Penicillin was administered at the rate of 20,000 units every three hours from the tenth to fourteenth day of disease. Hematemesis and tarry stools were noted on several occasions during this period. The significant physical signs remained limited to pulmonary rales, splenomegaly and semicoma." The patient was seen by the writers on the fourteenth day of disease at which time he was semidelirious and had temperature of 103.0° F., a pulse rate of 160, a white blood cell count of 1,650 and a hemoglobin of 6.3 Gm. per cent. "The findings on physical examination were essentially those listed at the time of admission. He was given an oral dose of 1.0 Gm. of fermentation type chloramphenicol on the fourteenth day and this was followed with 0.5 Gm. doses every 12 hours. The fever and pulse continued to range around 103.0° F. and 160, respectively. Forty-eight hours after treatment was started a state of shock developed. The pulse was of poor quality, the blood pressure was 90/40, hemoglobin was 4.4 Gm. per cent and the white blood cell count was 3,600. Moderate abdominal distention was noted without tenderness or rigidity. During the succeeding 24 hours he received two transfusions each of 200 cc. of whole blood. The chloramphenicol therapy was continued, and in addition, 20,000 units of penicillin were administered intramuscularly every two hours. The patient repeatedly vomited small amounts of coffee ground material and passed several small, tarry stools during this period. His condition deteriorated progressively; signs of pneumonia developed, shock continued despite the transfusions, the temperature fell, and the patient died on the eighteenth day of illness or the fourth day after treatment was instituted."

This patient had received his last 1.0 Gm. dose of chloramphenicol approximately 12 hours before death. "Specimens of blood, bile and spinal fluid taken at autopsy contained 13, 9, and 10 mg./cc., respectively, of chloramphenicol. Cultures of blood, bile and spleen obtained at post mortem yielded *S. typhosa*; the blood contained only a few viable organisms while the other specimens had appreciable numbers.

"Postmortem examination was performed by members of the hospital staff 10 hours after death. . . . The peritoneal surfaces were smooth and glistening. The cavity contained a few hundred cubic centimeters of serous fluid and, in addition, in the right iliac fossa there were several small masses of fecal material which totaled about 5.0 Gm. in weight. Careful examination, and questioning of the diener left little doubt that the fecal material was present at the time the abdominal cavity was opened. The wall of the terminal ileum, about 6 inches from the ileocecal valve, showed a perforation with a diameter of about 1 cm. The deficiency in the wall was plugged completely by a mass of inspissated feces which protruded from within the intestinal lumen.

"The intestine in the region of the perforation showed remarkably little evidence of inflammatory reaction of the serosa. Up to within about 2 cm. of the actual defect in the wall, the serosal surface glistened normally, but within this area the surface had lost its sheen and tiny dewdrop deposits were visible. The intestinal wall, for a few millimeters surrounding the margin of the perforation, was mottled with irregular small areas of hemorrhagic necrosis. A cut section through the intestine at the site of the lesion showed that the perforation occurred at an ulcerated Peyer's patch which presented the classic picture with a raised rolled mucosal edge and a crater bare of mucosa. The necrosis which had been visible through the serosa was confined to the base of the ulcer and surrounding ring of hyperplastic lymphoid tissue. Other Peyer's patches in the terminal ileum were hyperplastic but none was the site of sloughs or ulcerations. Solitary follicles were also prominent and several showed small pinpoint sloughs of the overlying mucosa.

"An appreciable amount of fresh blood was found by the diener when the ileum was opened." Examination failed to reveal any point of bleeding. "The stomach contained some coffee ground material; no point of bleeding was found in the stomach or jejunum.

"The remainder of the postmortem examination was essentially negative except for the presence of patches of bronchopneumonia, the finding of cloudy swelling in the myocardium and in the parenchymatous tissues of the liver and kidney, and acute splenic tumor."

The postmortem findings in this patient were of particular interest since they illuminated the pathological process in a treated patient with typhoid fever complicated by intestinal perforation which was unaccompanied by generalized peritonitis. "The intestinal wall beneath the ulcerated Peyer's patch had amazingly few infiltrating polymorphonuclear cells even though the necrotizing typhoidal reaction, and the subsequent slough, had laid bare the muscularis over a wide area and had penetrated to the serosa in a more limited area adjacent to the actual perforation." Since the normal anatomical relationships were disturbed when the writers first examined the intestine, it cannot be stated that the omentum had plastered itself over the defect. "However, the sharply circumscribed inflammatory reaction of the peritoneum indicated that this must have occurred. Even in the region of the local peritonitis the reaction was comparatively mild with relatively little fibrin and few polymorphonuclears; moreover, healing had begun as evidenced by the presence of fibroblasts."

"Other Complications: Complications of different types were noted in 3 other patients in the present series." One patient had been receiving chloramphenicol for three days and her temperature had dropped by lysis when she developed physical and roentgenological signs of bronchopneumonia accompanied by a fever of 103.0° F. "Chloramphenicol therapy was continued and, in addition, she was given 400,000 units of penicillin over a period of 28 hours. The patient became afebrile before the end of the course of penicillin and remained so thereafter; the physical and x-ray signs of pulmonary lesion disappeared over a period of four days."

One patient had intermittent attacks of auricular fibrillation on the eighteenth, nineteenth, twenty-first and twenty-third days of disease. "The patient was afebrile throughout this period. He received chloramphenicol from the eleventh to the twenty-first day of disease. X-ray examination of the heart during one period of fibrillation showed no enlargement; an apical systolic murmur was present during

the arrhythmias but disappeared during convalescence."

One patient who had no discomfort or fever during convalescence, is included in this section because laboratory examinations revealed evidence of urinary tract infection associated with *S. typhosa*.

Bacteriological Studies on Treated Patients.—In the current work, *S. typhosa* was not recovered from the blood of patients 24 hours after therapy was begun or subsequently except in 1 patient who died and in 3 patients who had clinical relapses.

"Before discharge from the hospital each of the 22 surviving patients in the present series repeatedly provided specimens of feces which did not contain *S. typhosa*. Cultural studies on 15 of the patients yielded negative results throughout the period of observation. Four persons had typhoid organisms in their feces before chloramphenicol was given but not in specimens cultured during or after treatment. Two patients excreted *S. typhosa* before therapy and on several occasions during or after drug was administered. . . . The last positive cultures from these 2 were obtained on the twenty-sixth and nineteenth days of disease, respectively." Stools from 1 patient were not cultured before specific therapy was instituted but negative results were obtained during and after treatment until the forty-fourth day of disease when a relapse began; repeated cultures taken during and after a second course of chloramphenicol were free of typhoid organisms. Two patients did not excrete *S. typhosa* during or after their relapses.

"Four patients in the present series had *S. typhosa* in their urine before treatment was started. Specimens from 2 of these did not yield pathogenic organisms during the periods of treatment or convalescence." Two patients whose urine was not cultured prior to treatment, excreted typhoid organisms on several occasions during the seventh and ninth weeks, respectively, after onset of disease. "These 2 were asymptomatic and afebrile at the time and their urines were normal except for the positive bacteriological findings. The bacilluria subsided promptly without additional therapy; cultures of specimens taken daily for a period of two weeks after the episodes yielded negative results. In the other patients of the present series, *S. typhosa* was not recovered during treatment or convalescence.

"Other Laboratory Observations: Widal tests employing type 'O' antigen were performed on samples of serum obtained from each of the patients early in the course of the disease and late in convalescence. The results of these tests . . . . were not considered in establishing the diagnosis of the disease. Only 6 of the 23 patients showed a rise in antibody titer during convalescence. The titers in 2 patients were consistently below 1/50 and in 2 others below 1/100.

"The hematological findings in this group of patients were consistent with those ordinarily found in indigenous tropical populations with typhoid fever. No toxic manifestations attributable to treatment with chloramphenicol were observed."

A New Mercurial Diuretic — RAVINA, A. — *La presse médicale*, 58: 856 (July 29) 1950.

All mercurial compounds used in proper doses exert a diuretic effect. This has been known for a long time since it was affirmed in 1741 and certain mineral derivatives of mercury were used at the end of the eighteenth century in the treatment of dropsy of cardiac origin. This diuretic effect, to be efficacious and prolonged, necessitated the use of large and consequently toxic doses. For this reason this form of treatment was abandoned until about 1920 when less irritant and more easily handled mercurial compounds appeared. These organic derivatives of mercury did not precipitate proteids and had only a slight local irritant action. They were not soluble in lipoids and hence nervous complications were avoided, they had little affinity for the tissues so were rapidly eliminated, and they could be used without fear of producing serious epithelial lesions of the kidney. However, it was necessary to use this medication with prudence, and it was not to be used in cases of albuminuria or uremia. Their action was of very short duration.

In general, there was a diuresis beginning one or two hours after an intravenous injection or two or three hours after an intramuscular injection. The maximum effect was reached in six to eight hours

and the amount of urine eliminated was 4 to 5 liters, sometimes 8 or 9 liters. The elimination of sodium chloride was greatly increased while that of calcium and potassium was much less. There was little effect on the other constituents of the urine.

There has been much discussion regarding the mode of action of these mercurial diuretics but it seems to be well proved that the mechanism of the provoked diuresis is of renal origin and that it is not due to mobilization of the tissue fluids.

Attempts have been made many times to prolong the action of the mercurial diuretics by associating them with other diuretic drugs or cardiac tonics. One writer proposed adding derivatives of the biliary salts, especially sodium dehydrocholate; the results seemed to be very satisfactory but this method has not come into general use.

The acidifying salts, particularly ammonium chloride and bromide, may also increase the action of the mercurial diuretics when they are given in daily doses of 6 to 10 Gm. Urea has the same synergic action and may even give better results.

There was greater progress when one advised associating theophylline with the mercurial diuretics. Compounds were made containing about 0.10 Gm. of the mercurial salt and 0.05 Gm. of theophylline. The addition of theophylline rendered the injections less irritant and less painful and also permitted administration in suppositories. The absorption of mercury was facilitated, the rate of diffusion was increased and the renal elimination and the rapidity of diuresis was augmented.

In spite of this progress, the use of mercurial diuretics was not without certain inconveniences or even dangers. A complete study was made of the toxic effects following the use of these diuretics and several cases of sudden death were reported occurring during or immediately after an intravenous injection. Experimental studies showed that these complications were due to a direct toxic action of the mercury which produced a sudden ventricular fibrillation. It was also found that the loss of chlorides due to the excessive diuresis might cause disorders of acute chloride insufficiency with muscular pains, stiffness, apathy, delirium sometimes followed by coma. Finally, there have been reported several cases of tetany which were rapidly cured by calcium.

Many investigations have recently been made in America with the object of combining the mercurial diuretics with new substances. Several writers have used the disodium salt of N(γ-carboxymethyl-mercaptomercuri-β-methoxy) propyl-camphoramic acid. The chemical structure of this new product is different in that the theophylline is replaced by sodium monothiol-thioglycollate. Each cubic centimeter contains the equivalent of 40 mg. of mercury. According to one writer this preparation has many advantages. Studies on cats showed it to be 160 times less toxic than the least toxic mercurial compound known. In addition, it causes practically no local irritation. It is not very painful, is easily accepted by patients and it may be injected subcutaneously. This mode of introduction is well tolerated in 90 per cent of the patients. In some cases it causes slight pain and may give rise to the formation of small nodules.

The results obtained are excellent. Six patients were treated with anasarca following heart failure. These patients had resisted prolonged rest in bed, digitalis, a dechlorinated diet and restriction of fluids. An injection of 2 cc. of this new mercurial salt produced diuresis in five minutes at a rate of 5 cc. per minute and persisted for two and one-half hours. The diuresis then diminished progressively but was still definite six hours after the injection.

Later 44 hospital patients were treated by subcutaneous injection with 86.6 per cent of successful results, 10 per cent of fair results and only 3.4 per cent of failures. It did not appear to be necessary to give intravenous injections. In fact, intravenous injections given to an equal number of patients gave slightly less favorable results. There were 35 outpatients with confirmed heart failure and edema who were given 1 cc. or 2 cc. of this diuretic once or twice weekly. The number of injections given varied from 1 to 38. Most of the patients received more than 4 injections. A total of 226 injections were given of which 205 were subcutaneous, 19 intravenous and 2 intramuscular. All of the patients treated improved and the subcutaneous injections were found to be especially efficacious in the reduction of the

edema and in the maintenance of the cardiac compensation. Only one patient had a general reaction consisting of slight chills, diarrhea and fever but the reaction only lasted for about two hours. One considers that subcutaneous injections of this new diuretic have an advantage over intravenous and intramuscular injections which have been used up to the present time. In most cases of edema they produce a considerable loss of weight without any appreciable toxic symptoms.

Several others have made a study of the same product and have reached similar conclusions. They also state the possibility of auriculoventricular dissociation, ventricular tachycardia and fibrillation after the use of the ordinary mercurial diuretics commonly used. Recent works have shown that BAL currently used in intoxications due to metals may prevent the appearance of all these complications but it completely inhibits the diuretic effect of mercury. Hence a search was made for something which would counteract the toxic action of mercury without hindering its diuretic action. This substance appears to have been found and is sodium monothiol-thioglycollate which has also been called M. T. 6. It can be given experimentally to amounts 160 times greater than the usual mercurial diuretics without producing any electrocardiographic effects.

This new mercurial diuretic has been injected subcutaneously to 100 cardiac patients and intravenously to 50 others. No serious reaction was observed. Electrocardiograms taken during the injection and at regular intervals of one minute later did not show any anomalies. Only 3 patients complained of a transitory local pain and 4 patients had rather high fever which was probably due to the distilled water used.

In other cases this product was given in subcutaneous doses of 2 cc. for five days without any signs of myocardial or renal irritation. The results on diuresis were excellent. In general, the elimination was not as great during the first 24 hours as with other mercurial diuretics but the effect was much more prolonged. In two or three days most of the patients lost several pounds in weight, sometimes as much as 8 pounds.

Experiments have also shown that the addition of ammonium chloride definitely increases the action of the drug. A combination of these two substances permits obtaining favorable results by injecting only 0.5 or 0.75 cc. of the mercurial diuretic.

Comparison of Mercurial Diuretics and Routes of Administration with Special Reference to Thiomerin — ATKINSON, WILLIAM J., JR. AND MULLIGAN, LEO V. — *Journal of Missouri State Medical Association*, 47: 583 (August) 1950.

"Most authors have noted about equal diuretic effects with equal doses of either Thiomerin, Mercuhydrin or Salyrgan-Theophylline."

Several reports have appeared recently on the advantages of Thiomerin. "This report is made because a fairly large series (226 patients) over a six month period has brought forth more unpleasant side effects than have been recorded previously."

"Subcutaneous Thiomerin.—Local reactions to subcutaneous Thiomerin were of sufficient magnitude to cause considerable discomfort in 35 per cent of 140 cases. These reactions may be divided as follows: 5 per cent had severe local reactions, 9 per cent had tender lumps or nodules for several weeks after administration, and 21 per cent had an uncomfortable sore arm for from several days to a week. Necrosis did not occur in any patients. Minor discomfort such as temporary burning, stinging and soreness occurred in an additional 12 per cent of the 140 cases. Two thirds of the moderate to severe local subcutaneous reactions occurred with the patient's first dose of Thiomerin and the rest of the reactions were scattered throughout the three months of treatment by this route. Sixty-five per cent of those who had more than mild reactions had subsequent reactions to subcutaneous administration. At least a part of this variation in response was thought to be due to variations in the drug since reactions were found to be more numerous with certain lots than others.

"It appeared that reactions to subcutaneous Thiomerin were more frequent if the drug was given into the subcutaneous fat layers than when given immediately

beneath the skin or beneath the fat. Sometimes it was difficult to avoid the fat layers, and technics of subcutaneous administration were undoubtedly quite variable since injections were given by a number of different physicians in the clinic.

"A majority of the patients who had local reactions were those with greater degrees of cardiac decompensation. Thus the status of the local circulation appeared to be a factor.

"Intramuscular Thiomerin and Mercuhydrin.—Intramuscular injections were avoided in those patients reacting most severely to the subcutaneous test dose.

"Little difference was noted in the per cent of reactions between intramuscular Thiomerin and Mercuhydrin. Considerable discomfort was experienced by 12 per cent of the 80 patients receiving Thiomerin in the deltoid muscle and mild discomfort by another 10 per cent. Mercuhydrin given in the deltoid muscle to 86 patients gave approximately the same per cent of reactions.

"Intramuscular injections in the gluteus maximus caused considerable discomfort in 4 per cent of patients with either Thiomerin (100 patients) or Mercuhydrin (107 patients) and mild discomfort in another 5 per cent.

"The patients who had local reactions to subcutaneous Thiomerin (except for a few of the most severe ones) were tested intramuscularly. Of these, 25 per cent had considerable discomfort in the deltoid muscle and 10 per cent had considerable discomfort in the gluteus maximus."

General Reactions.—"Little difference was noted except for a slightly higher incidence of nausea, diarrhea, and cramps in legs and abdomen with subcutaneous Thiomerin, and cramps with intravenous Salyrgan-Theophylline. In a group of patients treated at another hospital where the dry powder form of the Thiomerin was not kept refrigerated (this is said by the manufacturer to be unnecessary) 5 cases of diarrhea with cramps were noted, and 2 of these were bloody diarrheas."

A few of the most sensitive patients were eliminated from the Thiomerin series after their subcutaneous reactions, and the writers do not know whether they would have increased the per cent of Thiomerin reactions when other routes were tested.

"Comparative Efficacy.—Although some patients repeatedly obtained a better diuresis and weight loss on one particular mercurial than with the others, the average changes for the entire group showed about equal results for equal doses regardless of the mercurial or route used.

"As might be expected the subcutaneous route gave a slower, milder, more prolonged diuresis in comparison to the rapid diuresis produced by the intravenous route. Intramuscular routes gave results somewhere in between, with the gluteus maximus being more rapid than the deltoid."

"It would seem best at present always to test patients with 0.5 cc. doses of Thiomerin subcutaneously, and switch to the gluteus maximus muscle if local reaction occurs. Intravenous mercurials will still be necessary in some patients because of the discomfort caused by using other routes."

Dimercaprol in Acute Lead Poisoning — Bastrup-Madsen, Poul — *Lancet*, 2: 171 (July 29) 1950.

The writer reports here 2 cases of acute lead poisoning treated with dimercaprol.

Dimercaprol was given in the dosage of four doses of 0.1 mg. on the first day, two doses of 0.1 mg. from the second to the fourth day, and 0.1 mg. on the fifth and sixth days. "The preparation used was a 5 per cent solution of dimercaprol in arachis oil containing 10 per cent benzyl benzoate."

"Case 1.—A girl aged 15, had taken a teaspoonful of litharge (lead monoxide) to induce abortion, and nine days later a second teaspoonful. In the next few days she complained of increasing nausea and headache. Four days after the last dose of litharge she developed intermittent diffuse abdominal pain and was admitted to the writer's hospital.

"On admission the haemoglobin was 68 per cent; 0.2 per cent of stippled cells were found. The urine contained porphyrin. The amount of lead excreted in the urine was 0.11 to 0.14 mg. in 24 hours."

"During the first few days in hospital mild abdominal pain persisted, but it was so slight that it did not require treatment. The patient felt a little nauseated. On the third and fourth days in hospital the

patient was given ammonium chloride 6 Gm. daily, but did not respond with a definite increase in the excretion of lead. From the fifth day she was given a six day course of injections of dimercaprol, which led at once to a considerable increase in the excretion of lead in the urine. The patient suffered no discomfort from the treatment, and the increased excretion of lead was not accompanied by any rise in the number of stippled cells."

"Three months later the patient was well, and the haemoglobin was 80 per cent.

"Case 2.—A woman aged 32, had taken a teaspoonful of litharge to cause abortion. During the next 24 hours severe abdominal colic developed, and she was admitted to the writer's hospital.

"On admission she had intense pain, was delirious, and had hallucinations. She was pale, with cyanotic lips. Her abdomen was tender but soft; palpation showed contracted intestines. Her blood pressure was 140/160, pulse rate 60, and haemoglobin 78 per cent. Her urine contained porphyrin. There was slight haematuria but no albuminuria. An eight hour specimen of urine contained less than 0.05 mg. of lead; the amount excreted in 24 hours was therefore reckoned to be less than 0.15 mg."

"Dimercaprol therapy as previously described was then instituted. The excretion of lead in the following three 24 hour periods was examined, and a definite increase was found. At the start of the dimercaprol therapy the patient was lucid and oriented but complained of severe abdominal pain, which persisted for the next four days. It seemed as if the injections of dimercaprol neither aggravated nor mitigated the pain. Nor did calcium injections, nitroglycerin, or atropine affect the pain. Injections of morphine gave some relief. By the fifth day the pain had disappeared, and the patient felt quite well. At the end of the course of dimercaprol there was no haematuria, no albuminuria, and no porphyrinuria, but the haemoglobin was still reduced (67 per cent)."

It seems reasonable to prefer dimercaprol to lead-mobilising therapy with acidosis or parathyroid hormone, since the latter methods of treatment involve a risk of exacerbating the intoxication and are thus contraindicated in the early stages of lead poisoning. "Further, in mobilisation of lead by means of acidosis or parathyroid hormone the patient is exposed to the risk of protracted hypercalcaemia, which may very well have unfortunate consequences. Dimercaprol must be regarded as a rational and effective means of increasing the excretion of lead in acute lead poisoning."

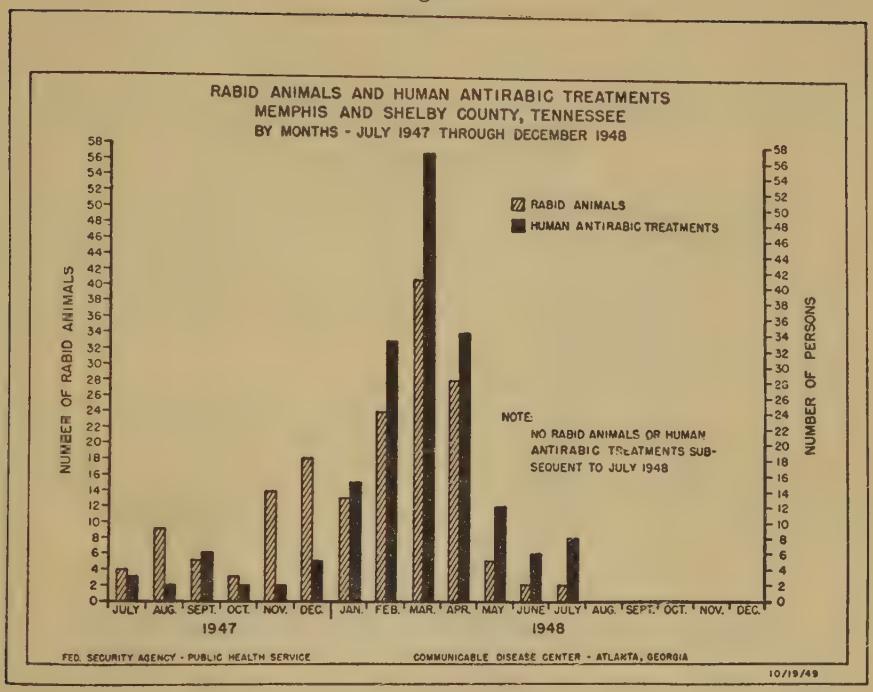
Effective Control of an Outbreak of Rabies in Memphis and Shelby County, Tennessee — TIERKEL, ERNEST S., GRAVES, LLOYD M., TUGGLE, H. G. AND WADLEY, SAMUEL L. — *American Journal of Public Health*, 40: 1084 (September) 1950.

It is the writers' purpose to report the experience of a local health department in the organization and execution of a control program in the face of an outbreak of rabies.

"Rabies incidence had been at a substantial endemic level in the dog population of Memphis and Shelby County for years. For example, from 1944 through 1947 the annual reported cases varied from 42 to 113 with the cases distributed persistently throughout each month of the calendar year. However, during the winter and early spring of 1948, the incidence began to reach epidemic proportions (Figure 1). By the end of March, positive animal cases were being reported at the rate of more than one per day. During the first three months, the number of cases was greater than twice that reported for the same period in 1947 and four times as great as in 1946. In the same quartile, over 105 persons had undergone the full series of antirabic vaccine treatments which far exceeded the number of treatments for a similar period of any previous year.

"When the number of cases began to mount in December, 1947, a strict dog quarantine was invoked throughout the county which required that all dogs be confined at home or walked on a leash when out of doors. Stray dog control was adequate with two dog patrol trucks and one alert car covering the city, and three trucks covering the rural county. Strays were impounded in the city's finely equipped, well staffed, and excellently managed Humane Shelter. A dog licensing law was in effect with 37,000 dogs under license at an annual fee of $1 per dog.

Figure 1


RABID ANIMALS AND HUMAN ANTIRABIC TREATMENTS
MEMPHIS AND SHELBY COUNTY, TENNESSEE
BY MONTHS - JULY 1947 THROUGH DECEMBER 1948
RABID ANIMALS
HUMAN ANTIRABIC TREATMENTS
NUMBER OF RABID ANIMALS
NUMBER OF PERSONS
NOTE:
NO RABID ANIMALS OR HUMAN ANTIRABIC TREATMENTS SUBSEQUENT TO JULY 1948
JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEB. MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC.
1947
1948
FED. SECURITY AGENCY - PUBLIC HEALTH SERVICE
COMMUNICABLE DISEASE CENTER - ATLANTA, GEORGIA
10/19/49

(Tierkel, Ernest S., Graves, Lloyd M., Tuggle, H. G. and Wadley, Samuel L.: *Am. J. Pub. Health*, American Public Health Association, Inc., September, 1950.)

"Rabid dogs were reported only by positive laboratory diagnosis based on direct smear examinations for Negri bodies. No animal inoculation test was performed on questionable and Negri-negative brains of animals clinically suspected of rabies."

Health department representatives met with the city and county commissioners to decide upon a plan of attack and formulate an official policy in connection with a program to combat the outbreak. "As a result of the discussions, it was recommended that an officially sponsored voluntary program be undertaken with canine vaccination as the principal feature.

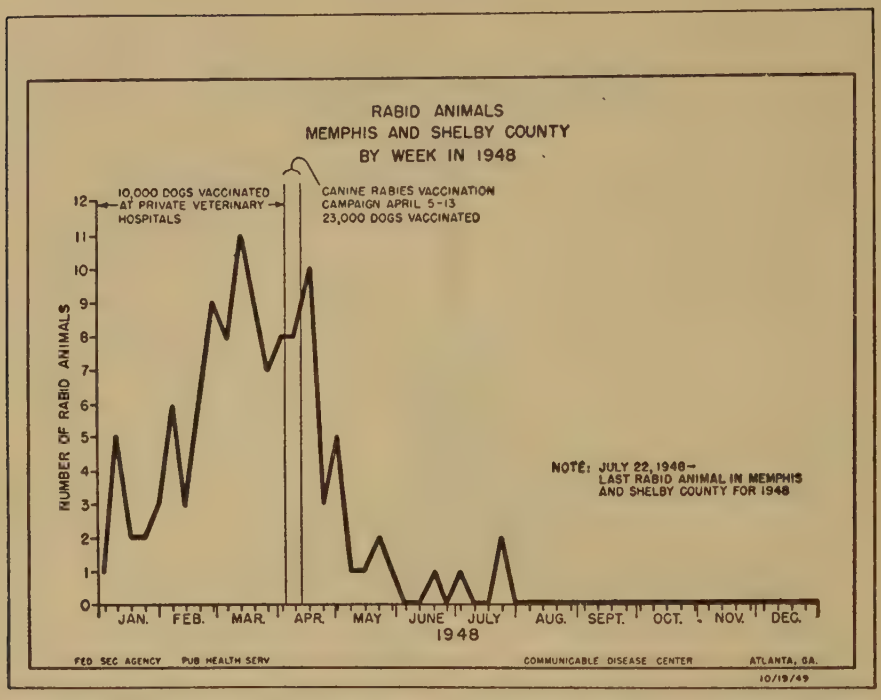
"After meeting with the licensed practising veterinarians of the city, machinery was set up for the operation of dog vaccination clinics throughout the city and county. All 15 veterinarians of Memphis and Shelby County offered to participate."

There were 36 emergency dog inoculation clinics held in the city for the three day period Monday, April 5 through Wednesday, April 7, and 35 clinics in the county, Saturday, April 10, and Monday and Tuesday April 12 and 13. "Besides these, the five established private veterinary hospitals were also available during the emergency campaign, making a grand total of 76."

"The veterinarians supplied and administered the vaccine during the one week emergency program at a charge of $1 per dog, regardless of dose, which was below the minimum charge for this service. Standard market phenolized veterinary vaccine was procured by the participating veterinarians from the usual commercial sources. Assignment of veterinarians to clinic stations was accomplished by drawing lots. Besides the veterinarian and his animal handler, each clinic was staffed by PTA volunteers and health department employees for the required clerical assistance. For each inoculation there was a uniform Health Department vaccination certificate made out in triplicate, with one copy for the dog owner, one for the Health Department, and one for the veterinarian."

"Public information and education was channeled through every available medium. The two newspapers most graciously gave liberal coverage throughout the campaign

Figure 2



(Tierkel, Ernest S., Graves, Lloyd M., Tuggle, H. G. and Wadley, Samuel L.: *Am. J. Pub. Health*, American Public Health Association, Inc., September, 1950.)

by carrying front page stories, daily spot maps of clinic locations, editorials, and editorial cartoons. News copy and advertising copy were issued every day. All radio stations carried spot announcements between their scheduled programs. Besides this, there were featured programs carrying interviews and round table discussions about the nature of the disease and the salient points of the Memphis rabies control program. Sound trucks cruised populous areas of the city directing brief reminders to dog owners. Letters and telephone calls went out to the clergy for announcements during church services. Placards were printed and distributed in all neighborhoods announcing the time and place of clinics. Mimeographed schedules of the clinics were distributed to city and county schools and to the public in the routine visits of public health nurses and sanitarians. Numerous talks were given by Health Department officials at schools, and civic and communal clubs, which were augmented by showing of the Communicable Disease Center filmstrip 'The Fight Against Rabies.'

"The public's response and the smoothness and celerity with which the entire program was executed was truly impressive. At one clinic station, 709 dogs were vaccinated from 11 A.M. to 5 P.M. by a single veterinarian. The campaign closed with 13,000 dogs vaccinated in the city and 10,000 in the county, a grand total of 23,000 in the one week program. With the 10,000 vaccinations done routinely by practitioners in the three months before the intensified campaign, it is estimated that approximately 80 per cent of the dog population was immunized.

"The entire program, which required only one week of preparation and one week of operation was conducted at the nominal cost of $450 to the health department, which included printing supplies, dog collection, personnel, and laboratory services for the two week period.

"The results of the program were more than gratifying. In the ensuing months, the positive cases began to drop until the last case of animal rabies and the last human antirabic vaccine treatment were reported in July (Figure 2). Both city and county

remained entirely free of rabies until March 10, 1949, when the first rabid dog since July 22, 1948, was picked up at the city limits. Seven and one-half months without a single case of rabies was a new and refreshing experience for Memphis.

"Despite the thorough dog control activities, it was not possible to eliminate rabies from the area until intensified mass immunization tactics were added to the emergency program of 1948. The results of this program stand as dramatic testimony to the importance of a well organized vaccination campaign."

Infection of Laboratory Workers with Coxsackie Viruses — SHAW, ERNEST W., MELNICK, JOSEPH L. AND CURNEN, EDWARD C. — *Annals of Internal Medicine*, 33: 32 (July) 1950.

Early in 1949, three workers in the laboratory, while conducting investigations with the Coxsackie viruses, developed febrile illnesses. "During the acute stage, a virus pathogenic for infant mice was recovered from the feces of all 3 individuals and from the pharyngeal secretions of 2 of them. During convalescence all developed in their serum a capacity to neutralize this virus which was not present prior to illness.

"These cases are presented because it is believed that they represent the first instances to be reported of infection with this virus in laboratory workers."

Patient 1.—The patient, a 26 year old white male physician, was admitted to the hospital January 11, 1949, with the complaints of fever, weakness, anorexia, malaise, headache and sore throat. "His illness had started on the evening of January 9, with malaise and anorexia. On the following day a dragging pain in the right upper quadrant of the abdomen developed which was present only on exertion. That evening while walking he had an episode of weakness, sweating, and near collapse. Fever was first noted on the evening of January 10.

"A review of his past history revealed a story of infectious mononucleosis in 1944, with persistent splenomegaly since that time. Over a period of years the patient had developed herpes simplex whenever he had fever. During a fever of unknown origin in 1945 which lasted three days, slight icterus was noted, but the results of additional liver function tests and of red blood cell fragility tests were normal. Subsequently, the icteric index varied from 10 to 25 without other evidence of liver malfunction.

"A physical examination on January 10 revealed a well developed and well nourished white male of 26, febrile and weak. The temperature was 104.2° F., pulse 120 and respirations 20. The only other abnormal findings were hyperemic conjunctivas and a nontender spleen palpable 2 cm. below the left costal margin. No adenopathy, skin rash, or abnormal neurological findings were observed.

"On January 11, the left tonsil became inflamed and enlarged with an ulceration containing a small amount of yellow discharge. On January 12, lesions of herpes simplex developed on the upper and lower lips. During exacerbations of fever which began on the fifth and seventh days of illness, the patient experienced malaise, headache, and pain in the midback. At no time was there nuchal rigidity or a positive Kernig or Brudzinski sign. The patient's temperature returned to normal on the tenth day of illness, and his convalescence was uneventful thereafter.

"Administration of 200,000 units of aqueous penicillin every eight hours was started on January 14, 1949, because a smear of the enlarged left tonsil was thought to reveal Vincent's organisms. There was no obvious effect of this treatment on the clinical course."

Laboratory Data: The total and differential white blood cell counts were normal. "A complete blood count and a urinalysis were normal on January 11. An x-ray of the chest on January 13 was normal. Tests of the serum on January 17 for sheep cell heterophil antibody and for agglutination of enteric organisms gave negative results. Blood cultures taken at the peaks of temperature remained sterile, and nose and throat cultures failed to grow any pathogenic organisms. Because the patient at no time had meningeal signs, a lumbar puncture was not done.

"The results of tests for liver function were as follows:

"On January 10, serum bilirubin determinations revealed a direct reading of 0.37

mg. per cent, a total of 3.94 mg. per cent. Cephalin flocculation was negative in 24 hours and 1 + in 48 hours. On January 12, blood serum total protein was 6.37 Gm. per cent with 3.26 Gm. of albumin and 3.11 Gm. of globulin. On January 17, serum bilirubin direct was 0.34, total 3.88. Cephalin flocculation was negative at 24 and 48 hours. Bromsulfalein retention at 45 minutes was 1.5 per cent. Thymol turbidity was 1.5 units, thymol flocculation was negative. Urine urobilinogen and urine bile tests were negative.

"Virus Studies: Specimens of feces obtained from this patient were prepared and inoculated into infant mice. . . . An agent which killed or paralyzed each mouse in 4 separate litters of 9 each, was isolated from a pool of feces collected on January 13 and January 15. This was passed by the intracerebral route through 4 generations of infant mice. The brain suspensions used in passage were shown to have an infectivity titer of 10^{-4} in the third passage. This agent was shown to be capable of passing through a glass-sintered disk, bacterial filter.

"Nasopharyngeal washings of January 11 were similarly shown to contain the virus.

"Neutralization tests were performed with the patient's serum and the strain of C virus referred to above. Serum drawn prior to illness on November 29, 1948 and an acute phase sample of January 13, 1949 failed to neutralize the virus. Specimens of serum obtained on January 26 and February 21, following recovery, both gave neutralization indexes larger than 1,000.

"The virus was not demonstrable in specimens of feces from the patient on February 7, and April 24, 1949.

"Patient 2.—A 34 year old white male investigator became ill on May 16, 1949 with a severe frontal headache. He was asymptomatic on May 17, but on May 18, because he began to have fever, malaise and bilateral low thoracic pain, he was ordered to bed at home. The chest pain was a dull ache, present constantly, but was more severe on inspiration. The pain and headache were more distressing during the temperature elevations. After May 21, pain occurred predominantly low in the left side of the chest and occasionally low on the right side. The pain gradually subsided and after May 28 only an occasional twinge was noted. The patient resumed partial activity on May 23 and was fully active by May 27.

"A review of his past history revealed no recent or similar previous illness. A physical examination on May 18 revealed a well nourished and well developed white male of 34, febrile and weak. His temperature (oral) was 101.8° F., pulse 84 and respirations 20. The only other abnormal finding was minimal faucial hyperemia. Subsequent physical examinations failed to reveal pleural friction rub, nuchal rigidity, splenomegaly, hepatomegaly, or other abnormalities.

"The total white blood count on May 18 was 8,000 with a normal differential count.

"Virus Studies: An agent which caused paralysis and death in inoculated mice was isolated from the patient's feces on May 19, 25, June 1, 10, and 13, 1949. An identical or similar agent was obtained on three different occasions from throat swabs taken on May 18, 20, and 31, 1949. Virus was not found in a pharyngeal sample of June 10. A specimen of feces obtained prior to illness on February 21, 1949 failed to reveal the presence of the virus.

"Two samples of serum obtained prior to illness on November 29, 1948 and February 21, 1949 did not neutralize the virus. Serum of May 18 showed a neutralization index of 10. Serum of May 26 showed a neutralization index larger than 1,000."

Patient 3.—A 24 year old white female laboratory technician started to work in the laboratory on February 1, 1949. "She had been in good health with no recent illness. On May 16, 1949 she accidentally contaminated her mouth while pipetting a 1 per cent suspension of virus.

"On the afternoon of May 21, 1949 the patient noticed malaise and moderately severe pain in the right lower chest and right shoulder region. The pain was most pronounced on walking and on inspiration. During the evening of May 21, a moderately severe frontal headache developed. Fever (temperature not taken) and chilly sensations occurred during the evening of May 21.

"On May 22, the malaise and chest pain persisted though to a lesser degree.

Her temperature (oral) that evening was 99° F. The headache was gone. On May 23, the pain in the right lower chest shifted to the right upper quadrant of the abdomen where it seemed to be superficial and was aggravated by sneezing or coughing. The patient did not feel feverish. On May 24, malaise and abdominal cramps were noted, followed by diarrhea that evening and the following day.

"A physical examination on May 25, 1949 failed to reveal any abnormalities.

"A white blood count on May 25 was 7,275.

"Virus Studies: Samples of feces of May 20 and May 24, 1949 both were found to contain C virus. An attempt to isolate virus from a throat swab of this patient obtained on May 19, 1949 gave negative results. Serological tests revealed no neutralization of virus by serum obtained on February 10 or May 23, 1949 but a neutralization index larger than 1,000 in the serum of May 26, 1949.

"Other Laboratory Personnel.—In addition to the studies on the 3 cases described above, specimens of serum from 27 persons associated with the Section of Preventive Medicine were tested for their capacity to neutralize the virus. The serum from 18 gave negative results. Four had a neutralization index between 10 and 100. Five showed a neutralization index of 1,000 or over."

The Bornholm Disease and the Viruses of Coxsackie — PLICHET, A. — *La presse médicale*, 58: 857 (July 29) 1950.

In 1930 there was an epidemic of myalgia among the inhabitants of several fishing villages on the island of Bornholm in the Baltic Sea to the west of Denmark and south of Sweden. This new disease occurred almost always at the end of summer and in the autumn, and was manifested by fever and by pains situated in the muscles of the thorax and in the abdomen. Deep respiration, coughing and laughing or anything causing movements of the diaphragm increased the pain, the point of election of which was situated in the last intercostal spaces and under the xiphoid appendage. In children the pain was often abdominal and sometimes there were transitory nodules in the muscles. The disease was almost benign and ended in four or five days except when there were relapses or complications such as pleurisy, otitis media or serous meningitis.

The disease soon became epidemic and from 1930 to 1934 more than 10,000 cases were reported in Denmark and more than 13,000 in Sweden. There was no doubt as to the infectious nature of this benign disease and in the ignorance of its causal agent various hypotheses were advanced regarding its pathogenesis since no autopsies were possible.

In 1932 one writer spoke of an acute primary inflammation of the diaphragm. Another attributed the pain to a benign dry pleurisy and, in fact, in certain cases the disease was complicated by pleurisy discovered by radiology. Other writers remarked that the pain was found especially in the territory of the last dorsal roots and that the possibility of an involvement of these roots by a neurotropic virus could not be eliminated, especially as this affection, in certain epidemics, is accompanied by a benign lymphocytic meningitis.

The disease did not remain localized to Denmark; it was in Sweden in 1932, and in 1933 a series of cases in Yorkshire was reported. It occurred in France in 1935 and then it passed on to America where it was noted in 1936. Since that time, short epidemics or sporadic cases have been reported in all countries. A series of 18 cases which occurred in the autumn has just been reported in England.

The symptoms have remained the same but headache seems to be more frequent and intense abdominal pains have caused operations to be performed erroneously for appendicitis or acute peritonitis. In other cases the pains have extended to the extremities and have resembled the preparalytic stage of poliomyelitis. It is probable that on account of its benign nature and the rapid course most of these cases are not recognized and the disease may be more frequent than is generally supposed.

At the present time this disease is of considerable interest because a certain number of authors believe that it may be caused by a virus of Coxsackie. In the United States and Canada, this name has been given to the viruses which were found in

patients living in the village of Coxsackie in the state of New York. These patients had nonparalytic poliomyelitis, influenza or epidemic myalgia and a virus transmissible to mice and hamsters was isolated from the stools, blood and nasal secretion. In these animals, inoculation of the virus caused paralysis within 48 hours and autopsies showed a proliferation of the cells of the sarcolemma with loss of striation of the voluntary muscles and in the diaphragm.

In Canada, this virus has recently been isolated from the stools of 3 children with typical poliomyelitis, from adults in contact with these children and also from the stools of a child having the syndrome of Guillain-Barré with an ascending paralysis of the Landry type. In some cases there have been isolated in the same patient, the virus of poliomyelitis and the virus of Coxsackie.

The virus of Coxsackie is not unique. Up to the present time five species have been isolated which are differentiated by the complement fixation reaction as well as by neutralization of specific antibodies. In England, several writers have found three viruses which are similar to the viruses No. 1, No. 2 and No. 3 which had been isolated in the United States, and they have tried to establish relations of cause and effect between these viruses and the disease of Bornholm. During the course of their laboratory studies, one of these writers had pains at the base of the thorax and in the back, the pains increased during the night and respiration became difficult. The pains were accompanied by a slight fever. After two negative examinations, on the fourth day of the disease the blood gave a positive complement fixation reaction with the No. 2 virus of Coxsackie which he had handled during the course of the investigations. In the same laboratory, an individual volunteered to be inoculated by the nasal route with a virus cultivated in mice. This subject did not give any reaction with the virus of Coxsackie before the inoculation. He had a sudden intercostal pain just below the right shoulder with a slight fever 46 hours later. The pain was increased by the respiratory movements and by coughing or laughing. The complement reaction was positive and remained so for 9 weeks, 72 hours after the onset of the disease.

Two other laboratory infections were reported with the same virus. There was a painful syndrome comparable to the disease of Bornholm. These authors also had occasion to examine the blood of patients with this disease during the course of small epidemics which occurred during the autumn of 1949 in Yorkshire, Surrey and even in London. All of these patients had a complement fixation reaction to the No. 2 virus of Coxsackie and only with this virus while 26 normal individuals and 6 patients with poliomyelitis and lymphocytic meningitis examined under the same conditions did not present any reaction. Naturally control examinations were made with the viruses of meningoencephalitis, the virus of poliomyelitis attenuated in mice, yellow fever, infectious hepatitis, etc.

From these facts it seems to be established that the inoculation, accidental in 1 case and voluntary in another case, of the No. 2 virus of Coxsackie can produce the disease of Bornholm which has been described under various names such as epidemic myalgia, epidemic myositis, epidemic pleurodynia, epidemic dry pleurisy and devil's grip. On the other hand, patients with this disease give a complement fixation reaction with the No. 2 Coxsackie virus and not with the No. 1 or No. 2 viruses.

These Coxsackie viruses and especially the virus No. 2, although they were discovered in patients considered to have poliomyelitis, must not be classified among the classic poliomyelitic viruses. The characteristics are not the same and the poliomyelitic virus is much more difficult to isolate than the virus of Coxsackie. However, these viruses closely resemble the virus of poliomyelitis and it is possible that they are attenuated forms.

At any rate, this resemblance of epidemic myalgia to diseases produced by neurotropic viruses offers a new insight on the etiology of a number of undetermined myalgias, intercostal pains, brachial neuritis, arthralgias following anginas and painful syndromes which cannot be explained and which have led to a tendency to attribute them to a zona without eruption.

Primary Carcinoma of the Lung — GRAHAM, EVARTS A. — *Diseases of the Chest*, 18: 1 (July) 1950.

"Primary carcinoma of the lung has shown a remarkable increase in the last half century, to become perhaps the most frequent visceral carcinoma in the male sex."

Apparently some exogenous carcinogenic factor, inherent in recent culture, must be responsible for this dramatic increase.

There is a possibility of cigarette smoking being one of the factors.

In 500 cases of proved bronchiogenic carcinoma it has been rare to encounter a man with a squamous (epidermoid) bronchiogenic carcinoma who had not been an excessive cigarette smoker for years, or at least who had not formerly smoked cigarettes excessively.

"The use of tobacco in other forms, as in pipes and cigars, appears not to bear the same important relationship. It would seem, therefore, that if smoking is an etiological factor, it is either the greater inhalation of cigarette smoke or something in the composition of cigarettes which contains the carcinogenic agent. Various possibilities suggest themselves, perhaps something used in the curing of the tobacco, insecticides employed during its growth, or maybe even something in the paper."

Squamous, or epidermoid, carcinoma is by far the most common lung tumor, and it is the one which has shown the striking increase. It is overwhelmingly a male disorder. "It arises usually in a major bronchus and it represents a transformation of adult epithelium into cancer tissue."

"By contrast the adenocarcinoma is a tumor which occurs about equally often in the two sexes, but slightly more in the female. It is much less common than the squamous or epidermoid type, and it seems to be influenced slightly, if at all, by cigarette smoking. There is considerable evidence that in at least many cases this tumor begins as a so-called bronchial adenoma. It seems to represent a transformation of embryonic epithelium into cancer tissue, rather than a change of adult epithelium into cancer cells as in the case of the epidermoid type. It is therefore to be regarded as an entirely different condition from the ordinary squamous cell bronchiogenic carcinoma."

In a typical case of primary carcinoma of the lung there is cough with blood-streaked sputum and a shadow in the x-ray which is generally seen as an uncircumscribed abnormal density in the region of the hilus. "These features are so commonly found in most cases that it is imperative to proceed with the necessary additional examinations. In fact, the burden of proof is on anyone who doubts the presence of a bronchiogenic carcinoma under such circumstances. Of course, there are many variations from this more or less typical clinical picture. For example, if the tumor arises in a small bronchus there may be but little cough and sputum with perhaps no expectoration of blood. In such a case the x-ray shadow is often spherical and rather sharply circumscribed at a distance from the hilus. In other cases the tumor arises in the apex of a lung and the first suspicion of its presence may come from the pain experienced by the patient because of the invasion of the brachial plexus or intercostal nerves. In still other cases the complicating infection of the tumor with its attendant fever may be the first symptom of illness noted by the patient; or again, more rarely, the presenting symptom may be from a metastasis in the brain or in a bone.

"Whenever suspicious evidence is present it becomes an urgent and compelling matter to pursue the necessary special examinations. Of these there are two which stand out as particularly important; bronchoscopy and examination of the sputum for cancer cells, preferably by the Papanicolaou method.

"Unfortunately, many tumors arise in bronchi too small or too unfavorably situated to be seen with the bronchoscope." Only about 60 per cent of them can be visualized adequately enough to obtain tissue for a biopsy. The additional examination of the bronchial washings and sputum will give a higher percentage of positive diagnosis, although actually, as in the use of the bronchoscope, in the writer's experience he obtains only about 65 per cent of positive results. "The advantage, however, of supplementing a negative bronchoscopic examination with sputum examination is that in some cases a posi-

tive diagnosis can be made in that way. Similarly sometimes a positive bronchoscopic diagnosis can be made although the sputum examinations have been negative. . . . There is a very great danger of reports of both false positives and false negatives when the examinations are made by one who is not thoroughly familiar with the cytology of the secretions which he is examining. The use of the bronchoscope should not be neglected even if a positive diagnosis has been made by sputum examination. Very valuable information can often be obtained by the use of this instrument which a study of the sputum alone will not yield. For example, there are the questions of the proximity of the growth to the trachea, the fixation of the carina, etc.

"After using all the standard methods of examination there will remain about 30 or 35 per cent of cases in which, in spite of a suspicious clinical history and suggestive x-ray films, it has been impossible to establish a positive diagnosis. . . . The best thing to do under such circumstances is to perform an exploratory operation. In most instances at operation the diagnosis can be readily established by direct inspection and palpation. If there is still doubt it is nearly always possible to remove some tissue for an immediate frozen section. Experience shows that when the clinical history and x-ray examination are suspicious the exploratory operation will nearly always reveal the presence of a carcinoma even when no positive evidence has been obtained by bronchoscopy and cytological examination of the sputum."

The operation of one stage total pneumonectomy has become by common consent the preferred treatment for primary carcinoma of the lung. "By this operation it is easier to remove possibly invaded lymph glands; and, by analogy with well established surgical principles in treating cancer of other organs, the disease is more likely to be eradicated by the removal of the whole organ than by the removal of only a part, as by a lobectomy. The high operative mortality in the early days of nearly 50 per cent has been reduced to one now of 10 per cent or less." In 139 consecutive operations of total pneumonectomy for carcinoma in a period comprising the last four years and seven months from January 1, 1945, to August 1, 1949, the writer has had 12 hospital deaths, an operative mortality therefore of 8.4 per cent. "Of more importance than the operative mortality in cancer of the lung is the question of five year freedom from recurrence." Twenty-eight per cent of the patients are free from recurrence after five years. "Of those with glands involved there have been 15 per cent of five year survivors."

The condition is curable if the operation is done early.

"One of the most distressing features of the whole problem is the large percentage of patients who present themselves with the cancer too far advanced for a successful operation." Although the writer has made an exploratory operation in about 40 per cent of the cases, he has been able to perform a pneumonectomy in only 25 per cent of the patients who present themselves with proved primary carcinoma of the lung. "In almost all cases the reason has been that the cancer was too far advanced. In a few cases the operation has not been performed because the patients were considered to be too bad risks for reasons of being too old, bad heart disease, etc." The oldest successful pneumonectomy was in a patient 75 years of age. "Very old people do not tolerate the operation well."

The features which in general lead one to decline to operate are (1) cachexia from advanced cancer; (2) evidence of nerve involvement, such as severe pain, paralysis of vocal cord (usually the left), and paralysis of the corresponding half of the diaphragm; (3) the presence of demonstrable metastases in other organs, notably the brain, liver, bones, etc.; (4) the presence of pleural fluid which is found to contain cancer cells; (5) extension of the growth into the wall of the trachea. "At exploratory operation very often the cancer is found to have invaded the large vessels or to involve the mediastinal glands to such an extent that obviously all the tumor cannot be removed. Again, sometimes the cancer is disseminated over the parietal pleura in small nodules." If, however, only a localized invasion of the chest wall is found, the writer prefers to remove that portion of the wall with the lung.

"The question of palliative pneumonectomy frequently arises. There is no doubt that a patient will become greatly improved after the removal of a cancerous lung which contains an abscess or a considerable amount of infection. In other cases, however, in which infection is not a prominent feature there is some doubt as to how much palliation will be accomplished when tumor tissue in large amount is left behind. Also, there always remains the possibility of making the patient more uncomfortable if the bronchial stump breaks open because of some cancer tissue which prevents its healing." The writer finds that in the majority of cases which he explores but does not remove the lung the conditions present, such as involvement of the great vessels, make the technical procedure of pneumonectomy impossible.

The Effect of Streptomycin on Tuberculous Meningitis—BRAINERD, HENRY D. AND EAGLE, HENRY R. — *Annals of Internal Medicine*, 33: 397 (August) 1950.

"Twenty-seven patients suffering from tuberculous meningitis have been studied to determine the effect of streptomycin on the course of the disease. . . . Patients were accepted for treatment with streptomycin on the basis of a presumptive clinical diagnosis of tuberculous meningitis founded on a thorough clinical, roentgenographic and laboratory study."

"The patients fell roughly into five groups, according to the course of the disease under therapy."

"Group I.—Treatment Failure: Nine patients died during the first four weeks of treatment without significant clinical or laboratory evidence of improvement."

"Group II.—Early Relapse: Eight patients showed initial favorable clinical and laboratory response but later relapsed and died while still receiving treatment. These individuals all survived more than eight weeks but died before the end of the five month therapy period."

"Group III.—Late Relapse: Two patients showed initial favorable clinical and laboratory response but maintained slight persistent evidence of infection after completion of the five month therapeutic period. These patients died 7 and 12 months, respectively, after the onset of meningitis."

"Group IV.—Arrest with Recurrence: One patient was free of all evidence of central nervous system infection following the completion of five months' treatment, but meningitis recurred 100 days later."

"Group V.—Apparent Arrest: Two patients were completely free of all evidence of meningeal infection at the completion of five months' treatment. These patients are apparently completely well 16 and 17 months after the end of the five month therapeutic period."

"For purposes of analysis, all patients who survived at least eight weeks after the beginning of therapy, whose spinal fluid sugar content became normal for more than two observations, and who manifested symptomatic improvement, were considered to have demonstrated therapeutic effect of streptomycin and are hereafter referred to as improved cases. Patients not fulfilling all of these criteria were considered to be treatment failures. Including those patients now under observation, 18 fall in the improved category and 9 are failures."

The age and sex of the patient apparently influenced the outcome. "The average age of improved patients was 8.7 years, with a range of 9 months to 42 years. On the other hand, the average age of the unimproved group was 31.2 years, with a range of 8 months to 58 years. Fourteen of the improved cases were under 12 years of age, while only 3 of the unimproved patients fell in this age category. Eleven of 13 females responded favorably, whereas only 7 of 14 males were improved. Actually, 6 of 9 treatment failures were males over the age of 23 years. While disturbance of the sensorium did not signify that the response would be unfavorable, 4 of 5 patients whose sensorium was normal at the time of institution of therapy made good responses to treatment.

"On the other hand, there was no correlation between the therapeutic result and the number of cells in the cerebrospinal fluid or the concentration of cerebrospinal fluid glucose, chloride, or protein. White, Negro and oriental races responded similarly in this series. The degree of abnormality of the neurological examination was likewise of no aid in prognosis. Of particu-

lar interest was the fact that, within the limits of this series, the duration of the disease before treatment had no apparent effect on the eventual outcome. The average duration of symptoms before the institution of streptomycin therapy was 13.5 days in the improved group, as opposed to 12.6 days in the unimproved patients. In this series, the presence of demonstrable active tuberculosis in the patient other than in the central nervous system did not seem to affect unfavorably the response to treatment. Of 18 improved cases, 17 had demonstrable active tuberculosis other than meningitis. Eight of these patients had miliary dissemination. Of the 9 patients in the unimproved group, 6 had other associated tuberculosis, of whom 3 individuals had miliary infection."

"Subjective improvement, if it occurred at all, began within the first two weeks of treatment, although all symptoms did not disappear until considerably later as a rule. Improvement in the patient's sensorium occurred early, but complete return to normal was somewhat delayed. While some patients maintained persistent abnormalities on neurological examination, those whose nervous system examination became completely normal did so within the first 11 weeks. The return of the cerebrospinal fluid glucose content to normal was usually an early event, but proved to be transient in some cases. A later drop in the cerebrospinal fluid glucose level was generally the first sign of clinical relapse, and in many instances was used as a signal for the reinstitution of intrathecal therapy. The disappearance of *Mycobacterium tuberculosis* from the spinal fluid, as evidenced by negative culture or guinea pig inoculation, occurred most commonly during the fourth and fifth weeks after the beginning of treatment. Although guinea pig inoculation appeared to be a more reliable index of the presence of the infecting organism than culture, both tests were sometimes negative at the time of death in fatal cases. . . . Fever usually persisted for over one month, but all patients who became afebrile did so by the end of the ninth week. The chloride content of the spinal fluid showed extreme variability in its time of return to normal. Abnormality of the protein content and the number of cells in the cerebrospinal fluid persisted for many months, even after treatment was stopped. Increase in protein and cells in the cerebrospinal fluid, as well as the appearance of predominantly polymorphonuclear leukocytes, was commonly noted after the intrathecal administration of streptomycin. Thus the time of return to normal of various abnormalities produced by the disease may serve as a guide to prognosis.

"The effect of streptomycin on the miliary lesions of the lungs was quite striking. Of 10 patients with miliary lesions, the chest roentgen ray became completely clear in 3 and improved markedly in 4 others. In 1 instance, miliary lesions of the choroid healed dramatically. Two instances of tuberculous osteomyelitis improved under treatment. One patient with tuberculous pneumonia evidenced marked improvement as judged by roentgen ray. One patient with renal tuberculosis maintained evidences of infection until her death, which occurred two months after the start of therapy. Two of 5 patients manifesting extensive fibrocaseous pulmonary tuberculosis showed improvement by roentgen ray. In patients dying after a considerable period of treatment, healing of the miliary lesions was often apparent before death."

"The daily dosages of streptomycin varied widely. From ½ to 4 Gm. were administered by the intramuscular route. The majority of adults received 3 Gm. daily; most children received 1 Gm. per day. On a weight basis the daily dosage of streptomycin varied from 12.9 to 130 mg. per Kg. of body weight. The median daily dose was 60 mg. per kilo. Of 13 patients below the median dose, 6 were improved and 7 were failures. Of the 13 patients above the median, 11 were improved and 2 were unimproved. Thus 77.7 per cent of treatment failures occurred in patients receiving less than 60 mg. per kilo per day intramuscularly. Sixty milligrams per kilo is equivalent to 4.2 Gm. per day in an adult weighing 70 Kg. although no adult in this series received more than 3.0 Gm. daily. Intramuscular injections of streptomycin were administered at intervals of three to six hours."

"The earliest patients in this study were subjected to daily intrathecal injections of streptomycin for three weeks. Although

therapeutic response was apparently satisfactory, evidences of irritation of the subarachnoid space prompted a reduction of the period of intrathecal treatment. Accordingly, an attempt was made to treat several patients with daily subarachnoid injections for one week. Even in those individuals who received only seven intrathecal injections and who made an initial favorable response, relapse later necessitated further intrathecal treatment. One patient was successfully treated with single, weekly, intrathecal injections for 14 weeks and is apparently well 4 months after the cessation of intramuscular therapy. One patient received no streptomycin intrathecally and apparently recovered, only to develop recurrent meningitis 100 days after the termination of 5 months of intramuscular treatment."

Although several patients had received one or two intrathecal injections of 100 or 200 mg. before coming under care, none was given over 50 mg. in an individual dose in the wards. "The daily intrathecal dose varied between a minimum of 12.5 mg. and a maximum of 50 mg. per day. Most patients received 40 mg. daily, with little variation according to the size of the patient. Consequently, the daily dose of streptomycin given by the intrathecal route varied from 0.4 to 9.3 mg. per kilo (except for the 1 patient who received intramuscular treatment only). Among the improved cases the average daily intrathecal dose of streptomycin was 2.35 per kilo. In the unimproved group the average daily intrathecal dose was 0.77 mg. per kilo. The maximum daily dose of the unimproved group was 1.1 mg. per kilo. Only 3 patients in the improved group received a smaller daily dose than the maximum in the unimproved group. The total amount of streptomycin instilled into the subarachnoid space varied from none to 5.05 Gm."

"Toxic effects presumably attributable to streptomycin were fairly frequent, although severe intoxication was uncommon. Local irritation at the site of intramuscular injection was almost uniform with early streptomycin preparations, but was rarely seen as purer preparations became available. Eosinophilia occurred in 3 patients but seemed of no consequence. One instance of dermatitis was encountered. Ataxia was noted in almost all patients, but they learned to compensate remarkably well. Although vestibular function remained disturbed, the patients did not appear ataxic under ordinary circumstances. Deafness occurred in 3 patients, 2 of whom were infants. In 2 of the 3, the hearing loss was transient. Blindness, which at least partially improved, was noted in 2 infants but may have been attributable to the disease process rather than the drug.

"Evidence of irritation in the subarachnoid space following intrathecal instillation of streptomycin was very common. Increase in pleocytosis, with a predominance of polymorphonuclear leukocytes, associated with increase in cerebrospinal fluid protein content, occurred in the majority of patients. A hemorrhagic spinal fluid appeared in 8 patients and was thought to be due to the streptomycin. Two patients developed a Froin syndrome, typical of subarachnoid block, after many months of intrathecal medication. Two patients developed motor weakness, sensory abnormalities, and disturbance of sphincter function. In 1 of these the process was transient; in the other, the abnormalities persisted for seven months until death from relapse of meningitis. . . . Tuberculosis alone may produce a transverse cord lesion, so that such serious abnormalities are not certainly due to intrathecal streptomycin administration. In 7 patients, cranial nerve lesions occurred, but were likely a manifestation of disease rather than drug intoxication.

"A direct relationship between high dosage, both intramuscularly and intrathecally, and toxic complications seemed apparent. Deafness and blindness occurred exclusively in patients receiving greater than the median intramuscular and intrathecal dosage. On the other hand, myelitis was encountered in 1 patient after the ninth intrathecal instillation of 0.4 mg. per kilo of streptomycin. Severe irritation of the subarachnoid space was ordinarily seen only after many intrathecal injections."

Pediatrics

Aerosol Streptomycin Treatment of Advanced Pulmonary Tuberculosis in Children — MILLER, JOSEPH B., ABRAMSON, HAROLD A. AND RATNER, BRET — *American Journal of Diseases of Children*, 80: 207 (August) 1950.

"By employment of the aerosol route of administration, extremely high concentrations of streptomycin may be introduced into the lungs without discomfort and without the consequent danger of toxic blood levels. This route of administration has a further advantage in that certain substances may be added to the streptomycin solution to alter favorably the local environment and increase the streptomycin effect on the tubercle bacilli.

"A study of the effectiveness of massive doses of streptomycin in a special diluent administered by aerosol for treatment of pulmonary tuberculosis is the subject of this report." The patients treated were 12 children with the more serious forms of pulmonary tuberculosis during the year July 1948 to July 1949.

"Methods. — Solution Employed: A therapeutic aerosol solution was made up as a vehicle for streptomycin, containing 0.1 per cent Triton A-20 (detergent), 2 per cent glycerin (for its stabilizing action on the mist) and a sodium bicarbonate diluent of *p*H 8. Sodium bicarbonate was chosen for the alkalizing agent because it is one of the main constituents of the body's own buffering system, it exerts a liquefying effect on mucus and it is readily inhaled in high concentrations without deleterious local or systemic effects.

"To test the in vitro effect of this solution and its various ingredients, a bacteriologic study was undertaken, employing a standard strain of tubercle bacilli resistant to 1,000 units of streptomycin per cc. This study revealed that the *p*H of the medium and the presence of Triton A-20 have profound influence on the effectiveness of streptomycin against resistant bacilli. As the *p*H of the medium was increased in the presence of 0.1 per cent Triton A-20, the resistance decreased from 1,000 units per cc. at *p*H 6.5 to 100 units per cc. at *p*H 7, to 10 units per cc. at *p*H 7.4 and no resistance at *p*H 8. The diminution and loss of resistance appear to be due to the combined effect of the Triton A-20 and the alkaline *p*H values, since other data have shown that neither factor alone exerts such profound effects. Of course, the full effect of Triton A-20 cannot be tested by this simple procedure, since such a test would require the presence of lipid caseous material under in vivo conditions." The results of the test verify the rationale and desirability of clinical studies of the solution as constituted by the authors in pulmonary tuberculosis.

"Technic of Therapy: Oxygen was used as the source of pressure to produce the aerosol because of its ease of control and availability. DeVilbiss No. 40 nebulizers were employed because of their uniform efficiencies and the safety from spillage conferred by their vertical necks. In the beginning, the technic described by Abramson and his associates was employed to standardize each nebulizer by its efficiency in delivering phenolsulfonphthalein so that the dose received by each child could be determined. This test was later omitted when it was observed that there was no significant variation in the efficiencies of the nebulizers tested.

"Two technics of administration were employed, depending on the age of the patient. It was seen that older children who were cooperative and intelligent enough to operate a Y tube could be treated in the usual manner for adults. This consisted in producing aerosol only on inhalation by manually opening and closing the Y tube in rhythm with respiration. An occasional child found it difficult to coordinate operation of the Y tube with his respirations in the beginning, but most children over 6 or 7 years of age soon learned the procedure.

"Certain modifications in the accepted technic were made for the patients of this age group (Fig. 1 A). One was the addition of a 3 inch (7.6 cm.) length of rubber tubing to the oral end of the nebulizer so as to extend the point of aerosol delivery about 2 inches (5 cm.) into the mouth. This prevented the baffling out of aerosol

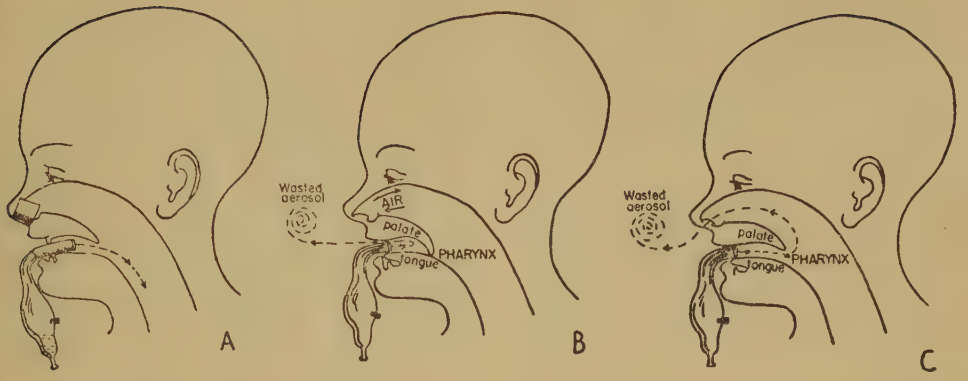


Fig. 1.—A, proper method of administering aerosol to older children. The nares are occluded and a rubber mouth piece is attached to the nebulizer. The mouth piece prevents baffling of the aerosol by the teeth or tip of the tongue. B, improper method of administering aerosol to older children. Failure to occlude the nares may result in closure of the lingual-palatal valve, with nasal breathing of atmospheric air and loss of aerosol from the mouth. C, improper method of administering aerosol to older children. Failure to occlude the nares may result in loss of aerosol through the nose owing to opening of the lingual-palatal valve. This can occur only if aerosol is mistakenly generated during the pause after inhalation or during actual exhalation. Occlusion of the nares eliminates these possibilities of error. (Miller, Joseph B., Abramson, Harold A. and Ratner, Bret: *Am. J. Dis. Child.* American Medical Association, August, 1950.)

particles by the teeth and tip of the tongue, avoided the risk of breaking the glass delivery end of the nebulizer by biting and provided a soft and slightly compressible mouth piece for the comfort of the relatively small mouths of children.

"Second, it was discovered to be necessary in most children to occlude the external nares with a band of adhesive tape, moist cotton tampons or sponge rubber plugs. When this was omitted, poor therapy often resulted from one of two circumstances. First, the child could effectively close off his oral cavity and simply breathe atmospheric air through his nose by bringing the dorsum of his tongue into apposition with his soft palate. This results in loss of almost the entire aerosol stream from the mouth into the atmosphere. (Fig. 1 B). On the other hand, the child could open this lingual-palatal valve during the pause after inhalation or during actual exhalation and cause the aerosol which might enter the mouth at those times to exit through the nose (Fig. 1 C). Of course, this can occur only if Y tube control is faulty. By occluding the external nares, the mouth is made the sole breathing orifice, Y tube correlation is simplified for the child and loss of aerosol through the nose is avoided. The observer can then be confident of good therapeutic technic, as confirmed by the absence of a cloud of mist about the patient's head.

"The infants, young children and older children who were unable to operate a Y tube were a special problem. It is hard for a nurse to operate the Y tube for a child because of the difficulty of judging the proper time to occlude the Y tube. The first method attempted was that of having the nurse simply tape the child's nose to insure mouth breathing and hold the continuously generating nebulizer in the child's mouth. This method was soon abandoned as it is wasteful of personnel time and results in the retention of only about 15 per cent of the streptomycin delivered.

"Next, each child in this group was treated in a commercial transparent oxygen therapy tent which covered the entire crib. The streptomycin blood levels with this method were insignificant or 0, owing to the large volume of air space which greatly reduced the atmospheric concentration of suspended streptomycin." The authors' observation of inefficient therapy with large tents agrees with that of others. "Progressively smaller tents and hoods were then used, with correspondingly progressive increases in the blood levels. Attempts were made to reduce the air space further by the use of various commercial masks designed for aerosol or oxygen therapy, but it was noted that the children would not tolerate such masks because of the pressure about the nose and mouth, the irritation of the external ears by the rub-

ber strap and the obstruction to the line of vision resulting from the high brims of the masks. These masks also showed a decided tendency to slip off the face, possibly because of lack of sufficient development of the bridge of the nose to anchor them in place.

"It was then apparent that the most efficient and acceptable device for infant use must be neither a mask nor a tent but a hood of the smallest size possible. There are several commercially available hoods for aerosol therapy of infants." Their expense, large size and low efficiency led one of the authors to devise a Cellophane face hood which is small, soft, efficient and inexpensive. "The hood consists of a bag or balloon of Cellophane covering the entire face. The perimeter of the hood encircles the anterior half of the head, running under the chin inferiorly, in front of the ears laterally and to the vertex of the skull superiorly. The hood is blown out like a balloon by the pressure of the oxygen entering it, so that it touches the patient only along its circumference."

"This hood is well tolerated by infants and small children because (1) it is of light weight, (2) it does not interfere with vision, (3) it does not exert pressure on the mouth or nose and (4) its straps do not touch the ears. The fastenings are secure so that slipping does not occur and frequent readjustments are not necessary. The patient need not lie down as with other hoods but may be propped up on a pillow or sit upright during therapy. One nurse may treat several children at the same time, thereby conserving personnel time. This face hood is of advantage because it is much more efficient than larger hoods, is inexpensive enough to assign a separate hood to each patient and can be disposed of after a course of therapy if desired. If it is preferable to use the hood indefinitely or for consecutive patients, it can be cleansed by washing in soap and water and soaking in an antiseptic solution.

"When the face hood is employed, one may observe the mechanics of respiration in relation to the aerosol stream. It is to be remembered that the aerosol is being continuously produced. Most children will accept the rubber mouth piece and thereby receive primary deposition of aerosol particles within the respiratory tract. If the mouth piece is not accepted, an L tube can be substituted to baffle out the larger particles and return them for renebulization. In either case there is at all times a high concentration of mist within the Cellophane face hood or actually within the mouth. Thus, the entire volume of tidal air—whether inhaled orally or nasally—is highly saturated with aerosol particles. If the side vent of the nebulizer is left unstoppered, the patient exhales air under slight positive pressure back into the nebulizer and out the side vent. This means that most of the aerosol being produced during exhalation is forced back and trapped out in the nebulizer, particularly the relatively larger particles. The smaller particles are lost into the atmosphere, as can be seen by observing the thin mist that emerges at the vent on exhalation.

"If a rubber tube of the same diameter as the vent is attached at the vent and coiled once or twice about the neck of the nebulizer so as to point away from the patient, the stream of exhaled air can be prevented from blowing against the patient's neck, and a small additional amount of exhaled aerosol can be trapped out in the tube. As this liquid gradually accumulates in the tube it tends to be drawn back into the nebulizer by gravity and by the negative pressure present at the vent during inhalation. Thus, much of the therapeutic material produced during exhalation is saved for renebulization. Practically all the active material is confined within the face hood, nebulizer and coil, so that no free aerosol can be seen in the room and the chances of contact sensitization of nursing personnel are slight. This was an important consideration, if only for psychologic reasons. . . . The blood levels obtained by this method are almost as great as those following therapy by older children who are able to control the Y tube and are higher than those resulting from the use of other tents, hoods and masks employed before this face hood was devised.

"This method is safe and effective for prolonged use. The open vent of the nebulizer serves as an additional breathing orifice, so that a temporary cessation of incoming oxygen or air causes no serious disturbance. The Cellophane bag can be seen to expand and contract partially with

each respiratory cycle, so that a method of observing respiration is available.

"Of the great number of small Cellophane hoods of various designs and lines of attachment that were tried, this one was settled on as the safest, most efficient and best tolerated. After the face hood was once applied to the face, the children felt no discomfort and could see all about the room, so that the initial apprehension was mild and short lived. After the first treatment or two, the children were perfectly relaxed and often napped during therapy. One infant who was at first too weak to sit up alone was propped in a semireclining position by means of a wooden inclined plane and took the treatment just as well as the other children.

"Dosage: The dosage of streptomycin employed in this study was 2 Gm. daily, administered in two doses of 1 Gm. each, for three to six months. Since streptomycin is more bulky and less soluble than penicillin, it was observed to be impractical to dissolve 1 Gm. in less than 5 cc. of diluent. In higher concentrations streptomycin tended to be deposited out during nebulization, thus occluding the capillary feed arm of the nebulizer. Even with this large volume of solution, the oxygen had to be humidified by bubbling through water to diminish the deposition of solidified streptomycin.

"After the 5 cc. was completely nebulized, at least 1 cc. of additional diluent was introduced and nebulized to rinse out the residual streptomycin adhering to the walls of the nebulizer. If solidified streptomycin was beginning to accumulate at the junction of the capillary tubes, the rinse was injected through the vent in a forceful stream to dislodge the solid particles. A short hypodermic needle (No. 27) was employed so as not to break the capillary tubes. If the feed arm was completely occluded by streptomycin, a dust particle or the tiny piece of rubber often picked up by a large hypodermic needle when it is pushed into a rubber-capped vial to mix the streptomycin, the feed arm had to be cleared out from above. This was accomplished by carefully injecting the rinse directly into the upper end of the feed arm, using a longer (No. 24) hypodermic needle.

"Administration of this large volume resulted in the delivery of about 95 per cent of the streptomycin from the nebulizer, as determined by comparative studies with phenolsulfonphthalein. The amount retained in the lungs was unknown and must have varied with the technics employed." One may state with some assurance that up to 0.36 Gm. of streptomycin per treatment may be deposited in the lungs with the present technics.

Blood Levels: The face hood technic results in higher blood levels than any other method employed, except actual Y tube therapy. Substantial (though probably not bacteriostatic) blood levels were obtained by aerosol administration and a single treatment resulted in a blood level of 24 hours' duration. The lungs evidently become saturated with streptomycin and release it to the blood stream slowly, so that the pulmonary tissues contain a high concentration for a long period. This is in contrast to the results of intramuscular administration of similar dosage, which gives a blood level that is higher but of shorter duration and a lung level that is relatively low and transient. It also contrasts sharply with curves for penicillin absorption following aerosol administration, since penicillin is absorbed more rapidly from the lungs than is streptomycin, resulting in a high penicillin blood level of short duration.

"The blood levels herein reported are not considered sufficiently high to influence the course of the disease. Their chief value is as an indication of the efficiency of aerosol technics. They are cited here because practically all previous publications on aerosol therapy of tuberculosis have reported that the administration of streptomycin aerosol does not result in demonstrable blood levels." The authors feel that their high blood levels have come from careful attention to technical details of aerosol administration, as well as employment of large volumes of streptomycin in high concentration for long therapeutic periods.

"Time Factor: The duration of each aerosol treatment was much longer than that ordinarily employed. Most aerosol treatments reported were of 10 to 20 minutes' duration." In this study, the Y tube technic required an average of one hour

of continuous therapy and some patients took even longer. "The second technic, in which aerosol was generated continuously into a face hood, required about 40 minutes. The importance of this factor is based on the obvious premise that, with all other factors equal, the volume of the intrapulmonary dose varies directly with the duration of exposure to aerosol."

"Clinical Results.—Toxicity: All 12 patients were completely free of sensitivity or toxicity reactions to either streptomycin or Triton A-20. In no instance was there any deleterious effect on the blood picture, blood chemical values or results of function tests of the liver and kidneys. Over the prolonged period of therapy, it was inevitable that a few disorders of the upper respiratory tract and contagious diseases occur; these included chickenpox in the 3 youngest patients. One child had a new fever (temperature of 102.5° F.) on the third day of treatment which subsided spontaneously after four hours. The fever did not recur, although treatments were continued without pause. A girl experienced an increase in her usual chronic cough for the first two weeks of therapy, but the cough disappeared completely after that time. Another child had three minor nosebleeds during the six months of therapy and one or two treatments were omitted after each episode, with no return of the bleeding on resumption of therapy.

"No mucosal or dermatologic manifestations of sensitivity occurred in any of the patients, despite the intimate exposure of the skin of the face, neck and hands and the mucosa of the nose, mouth and eyes. Nasal smears for eosinophilia turned positive during treatment for only 1 patient. The reactions of this patient remained negative to intradermal and patch tests for sensitivity to streptomycin and Triton A-20, as did those of all other patients, but he showed positive skin reactions to several inhalant allergens. He continued aerosol therapy without demonstrating clinical allergy."

"No reactions attributable to streptomycin occurred in any patients or nurses in the aerosol group."

"Description of Cases: The present series consists of 12 children with tuberculosis, varying from 8 months to 15 years in age. There were 3 with pulmonary cavitation, 1 with miliary tuberculosis with no evidence of active extrapulmonary lesions, 1 with tuberculous pneumonia, 3 with chronic exudative primary lesions, 1 with possible reinfection tuberculosis with apical infiltration and 3 with atelectasis of a segment, lobe or entire lung."

"Summary of Cases.—The first case was that of a 15 year old girl with a fresh and rapidly progressive cavitary lesion of the upper lobe of the left lung that responded to aerosol therapy with apparent healing. The second case was that of a 9 month old female infant with far advanced progressive primary tuberculosis of almost the entire left lung, which failed to respond adequately to streptomycin given intramuscularly and thiazolsulfone given orally, but which responded with apparent healing when aerosol streptomycin was added. The third case was that of a 7 year old boy with a chronic cavitary lesion of the apex of the left lung with clinical and roentgenologic response and apparent healing on aerosol therapy. However, his gastric washings continued to show occasional acid-fast bacilli during and after disappearance of the parenchymal lesion.

"The fourth case was that of a 1 year old male infant with miliary tuberculosis whose lesion responded favorably with apparent healing to aerosol therapy. The fifth case was that of an 8 month old female infant with tuberculous pneumonia of the upper lobe of the left lung, whose lesion also responded favorably to and apparently healed on aerosol therapy.

"The sixth case was that of a 7 year old boy with a reinfection type chronic infiltration of the apex of the right lung that slowly responded favorably and apparently healed with aerosol therapy. Three children (cases 7, 8 and 9) had chronic primary lesions which had not completely healed with conservative measures, but which slowly cleared up and apparently healed with aerosol therapy. The last 3 children (cases 10, 11 and 12) had chronic atelectatic lesions that showed no response to aerosol therapy."

Of the 12 children, the ones whose lesions failed to respond were those in whom the aerosol could not reach the site of disease; i.e., the atelectatic children. "Of the remaining 9 children, the disease in the 5 with the largest amount of fresh infiltra-

tion, cavitation and consolidation responded most favorably. The chronic infiltrative lesions of the 4 remaining children appeared to clear at a much slower rate and with more residual fibrosis."

A Comparison of "Symptomatic Treatment," Gamma Globulin, and Penicillin in the Treatment of Scarlet Fever — WEINSTEIN, LOUIS AND POTSUBAY, SAMUEL F. — *Journal of Pediatrics*, 37: 291 (September) 1950.

"The purpose of the work reported in this study was to make a detailed comparison of the effects of globulin and penicillin on the clinical course and laboratory findings in scarlet fever."

"Three types of treatment were used in this study. Alternate admissions of patients with scarlet fever, regardless of their age or the severity of the disease, were given globulin (one dose intramuscularly), penicillin in a dose of 15,000 units intramuscularly every 3 hours for 10 days, or only so-called 'symptomatic' treatment consisting of bed rest, throat irrigations, etc., as soon as the diagnosis was established. At the time of admission to the hospital, some attempt was made to grade the severity of the disease on the basis of the height of the fever, the extent and severity of the rash, the intensity of the pharyngitis, and the presence of such toxic manifestations as headache, nausea, vomiting, abdominal pain, and arthralgia.

"Globulin was administered in doses of 20 to 60 cc. depending on the size of the patient; no individual received more than 60 cc. of this material and only one injection was given. The plasma derivative was injected intramuscularly, great care being taken not to introduce any of it intravenously. When large doses were employed half of the total quantity was put into each buttock. At times analgesics had to be given in order to alleviate the persistent pain resulting from the intramuscular deposition of this material. Five different lots of globulin having potencies of from 30 to 80 antierythrogenic units per cc. were used. Patients who had had scarlet fever for a period longer than 48 hours were not admitted to the study."

"All patients were kept in the hospital for a minimum period of three weeks, while those who developed a complication or showed any abnormality in the course of their disease were detained for a longer period of time."

"Two hundred and fifty-five patients with scarlet fever were included in this study; of these 102 received 'symptomatic' therapy, 103 were given globulin, and 50 were treated with penicillin. . . . Although the age range of the cases varied somewhat in the three groups, the average for each was approximately the same. This should tend to rule out any important variation in the course of the disease solely on the basis of age difference."

An attempt was made to group the patients in this study with regard to the intensity of the clinical picture which was present at the time of admission to the hospital on the basis of the following criteria:

"Severe.—Temperature over 103° F., white blood count greater than 15,000, widespread rash with petechial and/or vesicular appearance, complaint of severe discomfort in the throat, marked edema, redness, exudate, and hyperplasia of the lymphoid tissue in the pharynx, and symptoms of severe toxicity such as headache, nausea, vomiting, and pains in the joints or muscles.

"Moderate.—Temperature between 101 to 103° F., white blood count from 10,000 to 15,000 per cu. mm., rash developing in typical order but not very bright and without petechiae, only moderate difficulty in swallowing, redness and edema of the pharynx but no exudate, and only slight or no symptoms suggestive of toxicity.

"Mild.—Temperature below 101° F., normal white count, rash quite sparse in distribution and light in color, discomfort in the pharynx minimal, redness of the pharyngeal mucous membrane only moderate without swelling or exudate; there were no signs of toxicity and in many instances the rash disappeared in about 24 hours. . . . Most of the persons in each treatment category were classified as having moderately severe infection. The distribution of severe and mild disease was also approximately equivalent, although the group receiving no specific therapy contained the smallest number of cases classified as mild. On the whole, however, in spite of com-

plete chance alternate selection, the patients receiving the various forms of therapy were quite comparable as regards both age and severity of their scarlet fever.

"Serologic typing of the beta-hemolytic streptococci isolated from the nose and/or throat at the time of admission to the hospital was successful in 228 patients. The organisms were classified both as to group specific carbohydrate and M substance, the determinations being carried out using the Lancefield technique. All of the organisms studied were found to belong to group A. No instances of pharyngitis due to other groups were observed in this study or in the ones to be described subsequently. . . . The commonest serologic types isolated during this investigation were 14, 18, 23, and 3. Seventeen other types were also demonstrated in the pharynges of various of the patients in this study. No correlation could be established between the serologic type of *Streptococcus pyogenes* responsible for the initial infection and the severity of the disease, the response to treatment or the risk of development of suppurative and/or nonsuppurative complications."

"The antibiotic agent produced return of temperature to normal about twice as speedily as either of the other therapeutic regimens. While practically all of the patients receiving penicillin had normal temperatures after four days, about 30 per cent of each of the other groups were still febrile beyond this time. Little difference in the rate of defervescence could be noted between those individuals given 'symptomatic treatment' and those treated with globulin; as a matter of fact, the plasma derivative seemed to be least effective in reduction of fever in the first 24 hours of treatment. These findings may be interpreted as indicating a much more rapid eradication of the primary focus of infection in the pharynx by penicillin than was produced by either of the two other forms of management. . . . In present day scarlet fever most of the fever is due to the local invasion by streptococci in the respiratory tract and not by the toxemia.

"In each group of patients, a varying percentage of individuals suffered a secondary rise in temperature after defervescence had been established for a period of at least 48 hours. In the group treated symptomatically or with globulin no correlation could be established between the second episode of fever and recurrence of streptococci in the pharynx since the majority of these patients retained the organisms in their upper respiratory tract throughout the entire period of observation. In those given penicillin a return of streptococci in the nose and/or throat did not always accompany the febrile recrudescence. In several instances, however, a recurrent pharyngitis with or without a scarlatiniform eruption was present. In 2 patients rheumatic fever was suspected."

"Marked differences were observed in the purely clinical responses to the various types of therapy. The group that fared most poorly from the standpoint of amelioration of signs and symptoms was the one which was given 'symptomatic' treatment. These patients had persistence of the pharyngeal discomfort for a period averaging six days; no difference was discernible in the rate of relief of sore throat in those treated with gamma globulin and those receiving no specific therapy. Penicillin, however, produced rapid relief of pain in the pharynx, most cases having lost all discomfort in from one to three days. The rash persisted for approximately the same length of time in penicillin-treated as in untreated individuals (an average of 4.5 days). In those receiving gamma globulin, the rash faded very rapidly and in most instances had completely disappeared in from 24 to 36 hours after administration of the material. This result could have been anticipated in view of the large amounts of antierythrogenic antibody administered in the globulin. Other toxic symptoms such as nausea, vomiting, and generalized aching were also relieved very rapidly by the plasma derivative; relief of these symptoms was more rapid with penicillin than with 'symptomatic' treatment, but the effect was not quite as rapid as that produced by gamma globulin.

"That penicillin was very effective in eradicating the primary focus of infection is borne out by the data relative to the rapidity of return to normal of the peripheral white blood count. . . . The average white blood count at the time of admission to the hospital was approximately the same in all three groups. Within one week, however, it had returned to normal

in those given penicillin but was still elevated in those receiving globulin or no specific therapy. . . . Most of the patients treated with penicillin were free of beta-hemolytic streptococci in the nose or throat within five days after initiation of treatment. Secondary increases in the number of peripheral white blood cells—those occurring after the count had been normal for at least three days—were almost twice as frequent in cases given gamma globulin or 'symptomatic' treatment as in those injected with penicillin. In some of the antibiotic-treated individuals the rise in white blood cells could be correlated with a recurrence of pharyngitis due to *Str. pyogenes*; in others, rheumatic fever or sinusitis was suspected while in some no cause for the recurrent leukocytosis was discernible. In the other patients secondary bacterial or nonsuppurative complications were responsible, in most instances, for the elevated white blood count.

"While it may be difficult to evaluate with great accuracy the results of treatment on such features as temperature, leukocytosis, rash, sore throat, and others, in as variable a self-limited disease as scarlet fever, the rate of disappearance of streptococci from the nasopharynx or other focus as a result of the application of a specific therapeutic regimen affords the most dependable measurement of the true effectiveness of therapy. Eradication of the organisms is most important since most of the suppurative complications of this infection probably depend on persistence of *Str. pyogenes* in the respiratory tract. Furthermore, from the public health standpoint, any form of treatment in scarlet fever is inadequate if it does not eliminate the causative bacteria from the primary focus completely so that the treated individual may return to his community without danger to others in his environment. The remarkable efficiency of penicillin and the relative inadequacy of the two other methods of management in this respect are well borne out by the data presented. . . . In the group given the antibiotic agent, 96 per cent of the patients no longer had demonstrable beta-hemolytic streptococci in their pharynx five days after first exhibition of the drug; the percentage free of organisms at the same time in the other groups was 7.84 for those receiving no therapy and 11.64 for those given globulin. The period of confinement in the hospital for practically all of the patients studied was 21 days, after which they were discharged to their homes and allowed to circulate freely in their communities." The ineffectiveness of simple isolation or even treatment with gamma globulin in reducing effectively the dangerous streptococcus carrier state was pointed out; about 51 per cent of those with symptomatic treatment and 36 per cent of those to whom globulin was administered were still harboring *Str. pyogenes* (group A) in the nose and/or throat at the time of dismissal from the hospital. "This is in marked contrast to the penicillin-treated group, all of whom were free of streptococci when they returned home and therefore could not serve as a seed bed for the dissemination of infection.

"In 14 of the patients who were treated with penicillin during the early phase of scarlet fever and in whom the streptococci had been rapidly eradicated from the nose and throat, bacteriologic relapse occurred after cessation of therapy. In some instances the recurrence of the organisms could be correlated with a new episode of pharyngitis, fever, or leukocytosis, but in some only a single positive culture was obtained although daily examinations were carried out. The explanation for this finding was, at first, not clear but . . . . this phenomenon was found, in the main, to be due to the admission of patients with acute scarlet fever to the same wards in which individuals who had been freed of streptococci by penicillin treatment were residing. In some instances sudden appearance of streptococci in the nose and/or throat of a patient could be traced to a house officer or nurse carrying the organisms. When patients were isolated on clean wards after five to six days of antibiotic therapy plus two negative throat cultures, and not allowed to mingle with fresh cases or personnel who were carriers, practically no instances of bacteriologic relapse were observed; when recurrence did take place on these 'clean' isolation wards it could practically always be related to a nurse or house officer who was a temporary carrier of *Str. pyogenes*."

"Further proof of the effectiveness of any agent used in the treatment of scarlet

fever is adduced from its ability to reduce markedly or even eliminate completely the incidence of early or late suppurative and nonsuppurative complications. . . . Several differences in the groups are quite outstanding. First, is the lack of suppurative sequelae in cases treated with penicillin; the high incidence of recurrent sore throat is probably the result of improper isolation of these patients once they were freed of their streptococci. . . . The relatively high rate of recurrent scarlet fever is probably the result of the action of two factors; one, the decrease in immune response to streptococcal infection following penicillin administration . . . . and the other, the matter of allowing these patients to come in contact with fresh cases of scarlet fever. . . . No instance of proved rheumatic fever was found in those who received penicillin, but 2 cases were classified as suspects." This elimination of rheumatic fever by penicillin treatment of the acute phase of scarlet fever is probably more apparent than real.

Gamma globulin exerted little if any effect on the development of suppurative or nonsuppurative complications. "While the plasma derivative contains a large amount of antierythrogenic material it probably has little if any antibacterial activity; even if it did, the high degree of type specificity of streptococcal bacterial immunity would mitigate against its being effective in a group of patients in whom scarlet fever was produced by a wide diversity of types. Suppurative otitis media was found three times more often in the group given 'symptomatic' treatment than in those receiving globulin. . . . Cervical adenitis with fever was present five times more commonly in individuals to whom the plasma factor was administered than in those who remained essentially untreated. . . . On the whole, no profound effect of gamma globulin in reducing suppurative sequelae in scarlet fever could be discerned." This material had no influence on the incidence of rheumatic fever. "The incidence of glomerular nephritis is usually low in scarlet fever (about 1 per cent) and the results obtained in this study are, therefore, probably not very valid since the number of patients in each group was relatively small. . . . In the present series of patients, the only instances of acute glomerular nephritis occurred in the group receiving 'symptomatic' treatment. While the impression may be created that both gamma globulin and penicillin given in the acute phase of streptococcal infection eliminate the risk of the subsequent development of acute hemorrhagic nephritis, this has not been borne out by later investigations."

Congenital Malaria. Report of 3 Cases — JONES, B. S. — *British Medical Journal*, 2: 439 (August 19) 1950.

Three cases of congenital malaria are recorded.

"Case 1.—An Englishwoman aged 29 had been resident in East Africa for some years, and was subject to periodic malarial attacks. She had arrived in Nigeria about one year previously, had taken suppressive quinine somewhat irregularly, but since arrival had had no overt attack of malaria. Her husband was English. She had 2 children, aged 6 and 4 years, her first labour having been prolonged and followed by subinvolution, the second being easy and normal. Throughout the present pregnancy she had been well, with the exception of one attack of cystitis. Her expected date was February 1, and she was admitted at 4:30 A.M. on February 11 with good pains, os dilated 2 fingerbreadths, a persistent occipitoposterior presentation, and premature rupture of the membranes. At 7:30 A.M. she was easily delivered of a healthy female infant. The maternal blood on admission showed no malaria parasites.

"The infant remained quite well till February 13, when it was observed to be fretful and to be vomiting after feeds. At 2 P.M. that day the rectal temperature was 102.6° F.; the mouth was healthy, the cord was clean, and the chest, cardiovascular system, and abdomen showed no abnormality, but the vulva appeared slightly inflamed, with a scanty thin purulent discharge. A blood smear was taken, and 5,000 units of penicillin intramuscularly three hourly and 0.125 Gm. of sulphathiazole six hourly were prescribed.

"At 10 A.M. next day the blood smear was reported to contain scanty subtertian rings, and 2 grains (0.13 Gm.) of quinine was given intramuscularly, and 1 grain

(65 mg.) of quinine orally three times a day was prescribed. At 4:30 P.M. the infant was very ill, with a poor slaty colour. At 6:30 P.M. there was a slight improvement; the spleen was found to be palpable and a further 2 grains of quinine was given intramuscularly. At 9 P.M. there were continuous convulsions and the condition was very poor. The infant, whose temperature was now 105° F., was sponged with tepid water, and 3 min. (0.18 ml.) of syrup of chloral was given, this being repeated at 9:30 P.M. At 11 P.M. convulsions had ceased, but diffuse moist rales were heard in the lungs: atropine, 1/600 grain (0.11 mg.), was given and oxygen administered by oral catheter.

"At 12:30 A.M. on February 15 the infant was asleep; the respirations were, however, irregular, and there appeared to be a one-in-three heart block. At 8:30 A.M. she was quiet, the pulse and respirations were regular, but the temperature, which had been sustained, was 104.4° F., and 2 grains of quinine was given intramuscularly. At 9 A.M. there was renewed respiratory and circulatory depression with cyanosis and occasional twitching of the upper limbs, and death occurred half an hour later. Necropsy was not performed.

"Case 2.—The mother, aged 37, and her husband were Europeans of French nationality. She had been resident in Nigeria for many years, and had had numerous bouts of malaria, though none recently, but took suppressive proguanil, 100 mg. daily. She had 3 children, the youngest aged 2½ years, and had had no miscarriages. All previous labours had occurred two or three weeks before the expected date, and all had been easy and rapid. She had been well throughout the present pregnancy and the expected date was March 4. Pains started at 5 A.M. on February 20. She was admitted at 6:30 A.M., and an easy rapid vertex delivery was completed by 7 A.M. The maternal blood showed no malaria parasites.

"The infant, a healthy female, was bottle fed from birth. The cord blood smear, taken at birth, contained scanty subtertian rings, and ½ grain (32 mg.) of quinine orally three times a day was prescribed from birth.

"At 2 P.M. on February 23 the baby appeared unwell and was vomiting. The rectal temperature was 101° F. At 11:15 P.M. 2 grains of quinine was given intramuscularly. At midnight the vomiting was more severe; it was accompanied by hiccup, a slaty cyanosis, and some twitching of the arms and eyes.

"At 1:15 A.M. the next day 3 min. of syrup of chloral was given. At 8:30 A.M. the condition had somewhat improved. The cord was separated cleanly, the chest and cardiovascular system showed no abnormality, but the liver edge was palpable and there was slight icterus. Quinine, 1½ grains (0.1 Gm.), was given intramuscularly. At 3:45 P.M. the temperature was 102.8° F., the jaundice was deeper, the liver was enlarged to 1 fingerbreadth below the costal margin, and there were diffuse bilateral moist rales. Penicillin, 5,000 units intramuscularly three hourly, was prescribed, but death occurred at 5 P.M. Permission for a full necropsy was not obtained, but a postmortem hepatic puncture smear showed scanty malaria parasites.

"Case 3.—A Scotswoman aged 29, the wife of an African, had been resident in Nigeria for one year only and took daily suppressive quinine. She had 2 children, aged 3 years and 1 year 8 months, both labours having been easy, and had had no miscarriage. She had been well throughout the present pregnancy apart from an attack of malaria three weeks before delivery, when she was treated with 0.1 Gm. of mepacrine orally thrice daily for one week. Her expected date was March 4. She was admitted at 11:15 P.M. on February 25, and an easy vertex labour was completed one hour later. Her blood on admission showed no parasites, but from February 27 to March 1 she had slight pyrexia (99 to 99.8° F.) accompanied by headache, which responded to a further course of oral mepacrine.

"The infant was a healthy half-caste male, and the cord blood at birth contained scanty subtertian rings. On the day of birth, February 26, 3 grains (0.2 Gm.) of quinine was given intramuscularly, and ½ grain thrice daily by mouth and proguanil, 25 mg. twice daily, were prescribed. Next day a further 3 grains of quinine was given intramuscularly. On the twenty-eighth there was slight pyrexia, but the infant seemed to be well and was taking his feeds. The chest, abdomen, and cardiovascular

system were normal, and the blood showed no malaria parasites. There was slight swelling of the left buttock, probably post-injection. Another 3 grains of quinine was given intramuscularly. At 4:30 P.M. the baby was unwell, with slaty colour and vomiting, and 2 grains of quinine was given intramuscularly. On March 1 there was rapid deterioration, with coffee-ground vomits, and death occurred at 5:30 A.M. Necropsy was not carried out.

"Subsequent to case 1 every expectant mother was prescribed, in addition to her customary daily suppressive, 400 mg. of proguanil daily, beginning 10 days before the expected date and continuing until admission in labour; a cord blood smear was also taken at every birth and examined for malaria parasites. Of the 37 deliveries, the first 6 were not cord tested: the 31 which occurred after case 1 were all cord tested at birth, and only cases 2 and 3 showed positive smears. Placental smears were not examined as a routine, as it was felt that the universal daily suppressive habit would certainly invalidate the results."

There have been a further 23 deliveries during July and August, 1949, all infants being cord tested at birth. "Of these only 1 showed parasites in the cord blood: a febrile illness developed within a few days of birth, but responded to treatment. A second infant, despite a negative cord blood, developed high pyrexia 26 hours after birth, and was tentatively diagnosed on clinical grounds and therapeutic response as a case of malaria."

"It is concluded that among nonindigenous European women of relatively low immunity, infected with the Lagos strain of *Plasmodium falciparum*, congenital transmission of malaria is by no means rare."

"There seem to be few effective precautionary or preventive measures. Thus regular suppressive procedures throughout pregnancy, here almost universal, did not seem to give reliable protection; nor, indeed, did a therapeutic course of proguanil, and in 1 case mepacrine, before delivery. It is, however, strongly urged that in the case of West Coast wives, whether delivered there or in the United Kingdom, the cord blood should be examined at birth as a routine."

Erythroblastosis Fetalis. Problems in the Interpretation of Changing Mortality in Erythroblastosis Fetalis — VAUGHAN, VICTOR C., III, ALLEN, FRED H., JR. AND DIAMOND, LOUIS K. — *Pediatrics*, 6: 173 (August) 1950.

The authors present a 12 year survey of mortality changes in erythroblastosis fetalis at a children's hospital and in a hospital devoted to obstetric care.

There were 349 cases of erythroblastosis fetalis at the Children's Hospital. "Included are four years (1937-1940) just preceding the discovery of the Rh factor, four years (1941-1944) during which the presumptive diagnosis of erythroblastosis could sometimes be confirmed by examination of the blood of patient and mother but sometimes not, and, lastly, four years (1945-1948) during which it has been generally possible to prove by laboratory tests the sensitization of the mother before delivery and to anticipate an illness in the newborn infant.

"The years 1945-1948 are divided into a two year period (1945-1946) in which exchange transfusion was not available, and a two year period (1947-1948) during which exchange transfusion has generally been available for babies admitted to the Children's Hospital within the first 24 hours of life.

"The arbitrary division of the clinical material into three groups, according to the age at time of admission to the hospital, brings out several important features. First, the most obvious effect of the discovery of the Rh factor (1940) was not a lowering in the mortality of erythroblastosis fetalis, but a tendency for patients to be admitted earlier in the course of the disease and in increasing numbers. For six years after discovery of the Rh factor the case mortality remained over 60 per cent in infants in whom the rapid development of clinical signs of erythroblastosis fetalis led to transfer to the Children's Hospital for treatment within the first 24 hours of life. The case mortality among infants admitted later in the first week remained about 35 per cent during this same period. Secondly, babies admitted after the first week of life have in all years had a good prognosis, if kernicterus were not present on admission. Of the 11 patients admitted

after seven days who failed to recover completely, 9 had developed kernicterus during the first week of life. Two patients were admitted moribund with anemia during the second week of life, and presumably might have been saved if admission had occurred earlier. The 7 per cent decrease in over-all mortality which occurred between the 1937-1940 period and the 1941-1944 period took place entirely within the group of infants admitted after the first week of life. Since a bad result in such infants was generally determined by the onset of kernicterus before entry, the outcome has not depended on methods of therapy except so far as simple correction of anemia has been concerned." In the babies admitted during the first week of life there was seen no difference in mortality, which suggests that the change in 1941 from the general use of untyped blood (usually Rh-positive) to the use of Rh-negative blood in therapy did not result in a generally lowered mortality.

When the results in 1947-1948 were compared with former years, it was seen at once that there has been not only a profound change in the nature of the clinical material so far as age at time of admission to the hospital is concerned, but also a concomitant and highly significant (by X^2) change in mortality of erythroblastosis fetalis, particularly in those patients admitted during the first day of life. "It cannot be assumed, however, that this fall in mortality rate was due entirely to the lifesaving properties of exchange transfusion. First, the great dislocation of patients (according to time of admission) into the group admitted on the first day has occurred at the expense of the groups admitted in former years only after two or three days. Accordingly, infants are now admitted early who, with the same illness in other years, would have been admitted later in the course of the disease, and these infants bring an inherently better prognosis to the group of infants now admitted on the first day.

"Also, in the period 1947-1948 many of the babies admitted on the first day (usually the first Rh-positive infant born to the mother after sensitization is detected) were admitted not for clinical erythroblastosis fetalis, as was always the case before the advent of exchange transfusion, but without clinical signs in anticipation of illness because the mother was known to be Rh-negative and sensitized. The results of the survey of the Boston Lying-In Hospital case material indicate that as many as 15 to 20 per cent of these patients admitted to the Children's Hospital on the first day of life during the years 1947-1948 would likely have had no illness (jaundice or anemia) of such severity as to be recognized as erythroblastosis fetalis. These babies would not have been transferred to the Children's Hospital if possible need for exchange transfusion had not been anticipated on the basis of demonstrated maternal sensitization during pregnancy. Accordingly, it seems quite clear that the mortality since 1946 cannot be compared to previous years as far as evaluation of treatment is concerned, since the clinical material is not comparable in the two periods.

"To complicate further the interpretation of the change in mortality during the years 1947-1948, the observation was made that even in the group of infants admitted after the first day but during the first week, where the mortality of bygone years was 35 per cent, a fall in mortality to 23 per cent has occurred. This is no direct result of exchange transfusion, since this procedure was not used in infants over 24 hours old during 1947 and 1948.

"Finally, it should be made quite clear that if exchange transfusion of a normal-appearing, though potentially sick infant, or of a more seriously ill infant with erythroblastosis fetalis, has been done within the first few hours of life, there are no criteria whatsoever which allow one to make an accurate appraisal of what the untreated course of the disease might have been, especially if the outcome is favorable. It is believed that failure to appreciate this fact has led to interpretations of the results of exchange transfusion therapy which rest on entirely untenable grounds."

There were 200 cases of erythroblastosis fetalis seen at the Boston Lying-In Hospital. "The four year periods, 1937-1940 and 1941-1944, and the two year periods, 1945-1946 and 1947-1948, have the same meaning here, as above, so far as developments in the field of study and treatment of erythroblastosis fetalis are concerned.

However, the clinical material studied differs in an important respect from that at the Children's Hospital; namely, that the patients comprise all Rh-positive offspring, including stillbirths, of Rh-negative sensitized mothers attending the clinic, whether the incompatibility is determined on clinical grounds alone (1937-1940), on clinical grounds supplemented by Rh typing (1941-1944), or on serologic grounds only (since 1945). . . . Since 1945 it has been recognized that many Rh-positive offspring of Rh-negative sensitized mothers have no clinical disease or such mild illness as to be within the limits of newborn variability." These babies comprise 18 per cent of all cases of erythroblastosis fetalis seen since 1945, and 24 per cent of the live born infants.

The observed over-all mortality of erythroblastosis fetalis in live born infants from 1937-1940 was 35 per cent, from 1941-1944, 38 per cent, from 1945-1946, 34 per cent, and from 1947-1948, 20 per cent. "The figures for the first two 4 year periods are manifestly not comparable to the later periods, since there should have been 10 or more Rh-positive infants in each period who, though born to sensitized Rh-negative mothers, showed no clinical illness. There were probably also a few infants in the period 1937-1940 whose clinical illness was interpreted as icterus neonatorum, sepsis, asphyxia or toxic hepatitis, because of less adequate means of diagnosis. In any case, there is no change in mortality between the 1937-1940 and 1941-1944 groups of infants to indicate that the change in 1941 to the general use of Rh-negative blood in therapy was of any fundamental benefit.

"Although the cases from the Boston Lying-In Hospital include all sensitized Rh-negative mothers in a large obstetric clinic, they do not represent from year to year a true cross section of the community so far as Rh problems are concerned. . . . In adjusting the data for this factor, the authors have considered as a referred case any woman who had her first erythroblastotic infant in another hospital. . . . The number of referred cases has increased since 1940 from about 20 per cent to about 40 per cent of the clinic load of sensitized mothers. The result of this . . . . has mainly been an increased number of stillborn infants with erythroblastosis fetalis, but not a significant change in the over-all prognosis for live born infants if the fact is taken into account that in referred cases there is a past history of erythroblastosis fetalis. The mortality in live born infants of referred mothers is high, but it is not significantly different from the outcome in the group of not-referred mothers who have had previous erythroblastotic infants, though there is a tendency to milder illness in the latter group. . . . In any case, these data give no reason to feel that a failure to observe a change in mortality in live born infants over the years is a reflection of the increased numbers of referred cases.

"The introduction of exchange transfusion, which in 1947 so profoundly altered the nature of the clinical material at the Children's Hospital, has had no such effect at the Boston Lying-In Hospital. There has been a continued slight increase in the proportion of referred cases in the clinic, without this having any important bearing on mortality in live born infants. The over-all mortality in live born infants was 33 per cent in 1945-1946 and 20 per cent in 1947-1948. This trend to better results in the last two year period has been observed both in the group of patients where there has been no previous infant with erythroblastosis fetalis in the family, and in the group where a previous affected infant has occurred. The difference might be interpreted as representing a specific effect of exchange transfusion in treatment during the latter period, but the observed differences are not statistically significant ($X^2 = 2.11$, $p = 0.1$)."

There is a large positive correlation between the likelihood of a bad result in a live born infant, particularly of kernicterus, and a shortening of the period of gestation to less than 38 weeks, particularly when the titer of maternal antibody is high (1:64 or more). During the past four years a practice of early induction of labor has increased the number of babies whose gestatory periods are less than 38 weeks in the Boston Lying-In Hospital. "For example, of 15 babies who developed kernicterus during the period 1945-1948, 9 followed labors induced, because of maternal sensitization, before 38 weeks' gestation."

During the period 1947-1948, while induction of labor per se showed no signifi-

cant correlation with the likelihood of a bad result, a gestation of less than 38 weeks showed a highly significant positive correlation at the Children's Hospital. "Analysis of these data has virtually eliminated the possibility that the observed effect of shortened gestation is simply the result of the fact that induction of labor was done to deliver a group of infants with inherently bad prognosis.

"The authors have long been aware of a possible detrimental effect of early induction of labor on the prospects of babies who might be live born at term, and for the last year of this study (1948) the policy at the Boston Lying-In Hospital with regard to early induction has been a good deal more conservative than before." The change in mortality of erythroblastosis fetalis seen in the years 1947-1948 has taken place entirely in the group of patients born in 1948, although exchange transfusion was used to about the same degree in both years. "Of the 5 cases of kernicterus seen in 1947, all were the issue of labor induced before 38 weeks' gestation, and 4 received exchange transfusion. The single case of kernicterus in 1948 was delivered by cesarean section at 34 weeks' gestation after the spontaneous onset of labor. No exchange transfusion was done. It seems altogether probable, therefore, that the improved mortality in the 1947-1948 period is no effect of exchange transfusion but represents the result of greater conservatism in regard to induction of labor in sensitized women."

"Caution is urged in assaying the value of any therapeutic measure, the use of which in erythroblastosis fetalis may result in a selected body of clinical material."

The Treatment of Whooping Cough with Nebulizations of Streptomycin — SERAPHICO, MARIO — *Boletim do Sanatório São Lucas*, 11: 187 (June) 1950.

When a new method for the treatment of whooping cough is discussed, it is done so with reserve. This is reasonable considering the great number of cures that have been presented for this illness which constitutes a constant problem to the pediatrician, without an absolute cure among them. However, the author points out that, in view of the number of cases and the results obtained by the use of streptomycin, at least some conclusions are to be permitted as to its effectiveness in the treatment of whooping cough.

With the appearance of streptomycin, various in vitro and in vivo experiments were carried out to determine and verify the action of the new antibiotic on *Hemophilus pertussis*. The results were so encouraging that many reports were published on the subject. One case, for instance, in which streptomycin was used by the aerosol method, was reported as having improved rapidly with an absolute cure at the end of 10 days. In another report studied by the author, streptomycin was administered intramuscularly and by the aerosol method.

From these cases the following conclusions were reached: Streptomycin appears to be an effective therapeutic agent in the treatment of whooping cough; administration by aerosol gave rapid and satisfactory results; no intolerance was observed after a week of treatment.

Taking these reports as a basis, the author decided to try streptomycin. Although the aerosol method, as disclosed in these reports, was the most effective, it was impractical in his own practice since it required that the patients be hospitalized. He decided, therefore, to use the DeVilbiss atomizer since it would present no complications of a technical nature and would permit the use of streptomycin without the necessity of oxygen.

A solution of the same proportions as had been recommended for the aerosol treatment was employed; namely, 2 Gm. of streptomycin were dissolved in 20 cc. of physiologic saline solution. The nose and throat of the patient were sprayed with this solution every four hours.

Of the 30 patients the author reports on, 7 were not clinically diagnosed. In the other 23, however, the diagnosis was confirmed by pertussis cultures and hemograms. A before and after comparative study of the hemograms, which the author thought vital to a proper evaluation of results, failed due to the lack of cooperation of the mothers who did not want to subject their children to another prick of the needle after they had been cured.

The ages of the patients ranged from 4 months to 8 years; the treatment was

started in various periods of the evolution of the infection, from five days to one month after its beginning.

In all of the cases, except 2, the total dose used was 2 Gm. of streptomycin. It was not possible to determine the exact daily dose, due to the method employed. It was certain, however, that the daily dose was less than ¼ Gm. since the solution prescribed lasted about 8 to 10 days.

The results of the treatment were good. On the second day after initiation of the treatment, coughing diminished and disappeared at the end of 8 or 10 days. In only 2 cases did treatment have to be continued for 18 days before recovery was complete.

The author points out that the efficacy of nebulizations of streptomycin in the treatment of whooping cough can only be definitely established by further study, observation, accurate diagnosis and the determination of adequate dosage, as well as the mechanism of the action of the drug.

A Note on the Treatment of Diaper Rash with Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Roccal) — PFEFFER, WILLIAM, JR. AND SMITH, CLEMENT A. — *Journal of Pediatrics*, 37: 351 (September) 1950.

"The ideal treatment for ammoniacal dermatitis (and, presumably, the ideal prophylaxis) would seem to involve impregnating the diaper with some nontoxic, nonirritating substance capable of inhibiting ammonia formation. The substance used should be cheap, easily available, and easy to prepare for use. A mixture of high molecular weight alkyl-dimethyl-benzyl-ammonium chlorides has been commercially available for some time under the name Roccal. It has been used extensively for disinfection and sanitization. It is easily available and of relatively low cost. The present study was undertaken to evaluate the use of Roccal in the treatment and prevention of diaper rashes."

"The antibacterial activity of Roccal was tested against Proteus OX_2, a standard organism with known urea-splitting activity. By the tube method . . . . complete inhibition of growth was observed after 10 minutes' exposure to a solution of Roccal diluted 1:30,000; after 5 minutes' exposure a 1:20,000 dilution was required.

"Using a saline suspension of normal infant stool as the test inoculum, the tube method showed a complete inhibition of growth after exposure for 10 minutes to a 1:20,000 dilution of Roccal.

"By the cup method, using a 15 mm. porous cup, a zone of inhibition of the growth of Proteus OX_2 was produced by Roccal at a dilution of 1:5,000, but no inhibition using a dilution of 1:10,000. When a saline suspension of normal infant stool was used as the inoculum, inhibition was found with Roccal diluted 1:1,000, but not with a dilution of 1:5,000.

"The tube method is reputedly more accurate, and certainly gives a closer approximation to the conditions obtaining in the diaper than the cup method. On the basis of these tests, a solution of Roccal diluted 1:5,000 was selected as of more than adequate strength for inhibiting ammonia formation in the diaper.

"Since the active substance is present in standard strength Roccal as commercially available in a 10 per cent solution, a 1:5,000 dilution results from diluting 1 part of the commercial preparation with 500 parts of water. The dilution of Roccal used for rinsing the diapers is of course only an approximation of the final dilution in the diapers since the volume of urine in which the Roccal redissolves is a variable."

"Skin testing previous to the use of Roccal therapeutically was carried out by applying a 2 inch by 2 inch gauze patch moistened with a 1:1,000 dilution of Roccal to the backs of 100 infants aged 1 day to 2 years. The patch was left in contact with the skin for 24 hours. No reactions of any kind were noted either at the end of the 24 hour period or after 48 hours. No irritation was noted in any of the 145 patients in whom Roccal was used therapeutically or prophylactically."

"The mildest form of ammoniacal dermatitis is an erythema of all or part of the diaper area. Further progression of the lesion leads to blistering, crusting, and ulceration. When the rash has persisted for several weeks or months, it assumes a chronic character with indolent ulcers having indurated borders, dark red papules, and, if general hygiene is poor, pustules. Healing is accompanied by transient brown pigmentation and in the most severe cases,

by scarring. A special characteristic in circumcised male infants is the formation of superficial ulcers with crusting about the urinary meatus and over the glans penis. This may be the only manifestation of ammoniacal dermatitis. It usually gives symptoms of severe pain and bleeding on urination, and sometimes produces urinary retention because of the pain on voiding.

"In the present series, the diagnosis has been restricted to patients displaying a typical rash restricted to the diaper area, without diarrhea and without evidence of other disease. The majority of the mothers spontaneously offered the information that the diapers smelled of ammonia. No infant was included who had had any response to another method of treatment although in the majority other therapy had been unsuccessful."

"All patients were treated in the same fashion. The mothers were instructed to use no other medication such as antiseptic powders, ointments, or diaper rinses. The diapers were washed and rinsed as usual, using a good nonionic synthetic detergent instead of soap, which reduces the bactericidal power of Roccal and of all similar antiseptics. Immediately before drying, the diapers were given a final rinse in Roccal solution, prepared in a dilution of 1:5,000 (1 teaspoonful of 10 per cent Roccal to 2 quarts of tap water), wrung out, and hung up to dry. Diapers prepared in this way were indistinguishable from diapers prepared without Roccal, in color, softness, and odor."

"An attempt was made to prevent diaper rashes in a group of 90 incontinent, nonambulatory infants and children in a state mental institution. These patients were kept in two pairs of wards, each of the pairs being comparable to the other in numbers, types of patients, and amount of nursing care available. The patients were all infants with an easily recognizable defect, such as mongolism or microcephaly, or older children with obvious severe motor and mental retardation.

"The diapers were cleaned by commercial laundry methods, and were the same for each of the four wards, with the exception that Roccal solution 1:5,000 was used as the final rinse in the diapers used in one ward of each pair. The other two wards served as control groups.

"Even before the test period about 10 per cent of the infants and 50 per cent of the older children had various lesions of the buttocks ranging from mild erythema to severe ulceration and chronic infection. For a period of three months Roccal was used in the diapers of the test group, and examinations of the patients in both test and control groups were made twice weekly.

"No significant changes in the existing lesions were noted in either group over the three month period. In both groups, many patients at one time or another had transitory periods of erythema, some with inflammatory maculopapules, but there did not appear to be any difference between the prophylactically treated and the control groups. At no time in either group, however, did there appear the typical blistered or acutely ulcerated rash of ammoniacal dermatitis.

"It seems likely that most of the rashes in these patients were due to nonspecific irritation and the nutritional and hygienic difficulties incidental to gross mental defects. The conditions of this trial are certainly not applicable to the prevention of diaper rashes in normal infants. Of the cases to be discussed below, in which diaper rash was treated by Roccal, 8 recurred after cessation of therapy. In each case, reinstitution of Roccal therapy was again effective, and the effect was evident as long as the treatment was continued. It appears that in these cases at least, Roccal would have been effective in preventing the rash completely. The use of Roccal to prevent recurrence was continued for one month in 1 case without harmful effects. For these reasons, it is felt that the use of Roccal to prevent diaper rashes in normal children in usual circumstances would be successful."

"Roccal impregnated diapers were used in the treatment of 64 infants with diaper rash. . . . Nineteen of these were mild and all were cleared in less than one week of therapy, most in less than five days. There were 28 cases considered moderate, all with acute inflammation and ulceration; 25 of these were completely clear at the end of one week, 2 cleared after two weeks, and 1 failed to respond. Sixteen cases were considered severe, and showed ulcers

with indurated margins, thick maculopapules and some pustulation. Most of the severe cases were also chronic. Healing in the severe cases was difficult to evaluate since pigmentation, healing of deep ulcers, and scarring, all tended to persist after the rash was quiescent. In the 16 severe cases, however, inflammatory changes were gone after one week in 12 cases, after two weeks in 3 cases; there was no response in 1 case."

Poliomyelitis and Immunization Against Whooping Cough and Diphtheria — BANKS, H. STANLEY AND BEALE, A. J. —*British Medical Journal*, 2: 251 (July 29) 1950.

"Inquiry into the cases of poliomyelitis admitted to one London hospital during the years 1947, 1948, and 1949 showed a total of 111 paralytic cases of all ages admitted during the period. Of these, 14, all under 5 years old, had a paralysis of the limb which had received one or more of a course of immunizing injections within the previous two months. The interval between the last injection and the onset of paralysis in the majority of the cases was between 9 and 14 days. The paralysis followed combined pertussis and diphtheria (A.P.T.) prophylactic in 9 cases, pertussis vaccine alone in 1 case, and diphtheria prophylactic A.P.T. alone in 4 cases. The paralysis, whether of arm or leg, conformed in general to a uniform pattern. It was not associated in time or place with any particular clinic or technique."

It is pertinent to mention two facts. "First, the incidence of poliomyelitis in England and Wales, including London, in 1947 and 1949 was the highest on record, but was much lower in 1948 (18 and 14 per 100,000 population in 1947 and 1949 and 4 per 100,000 in 1948). Secondly, the number of young children immunized against diphtheria and whooping cough was at a high and increasing level during these three years. There can be little doubt that there would be frequent overlapping of these occurrences, and that many children would be likely to be immunized at a time when they were actually infected with the poliomyelitis virus, although showing no clinical signs of it."

Table I shows the preponderance of lower limb paraylsis in the group who were not immunized or who were immunized over six months prior to onset of poliomyelitis, and the preponderance, on the contrary, of upper limb paralysis in the group who were immunized within two months of onset of poliomyelitis. "This latter group with 1 exception consisted of cases in which the same 'double event' occurred; namely (1) inoculation for whooping cough, diphtheria, or both combined; and (2) within two months of one of the injections in the course, the onset of poliomyelitis with paralysis of a practically uniform pattern in the same limb. In the upper limb it was the muscles of the shoulder girdle (deltoid, spinati, and pectorals) and the biceps and triceps which were invariably the first to be paralysed, and were often the only muscles seriously paralysed, although weakness was not uncommon also in the neighbouring muscles of the trunk and forearm. Occasionally the other arm was also, but less extensively, affected, and in 1 case the paralysis starting in the inoculated arm rapidly became general and was fatal. In the lower limb the pattern was similar. The muscles of the inoculated buttock and thigh were the

Table I.—Incidence of Paralysis in Upper (U) and Lower Limbs (L) in Relation to Immunization History

	1947		1948		1949		Total	
	U	L	U	L	U	L	U	L
No immunization history	7	9	3	1	7	12	17	22
Not immunized or immunized over 6 months before	7	15	2	4	11	24	20	43
Immunized within 2 months								
(*a*) Total	5	0	3	1	4	2	12	3
(*b*) Inoculated limb	5	0	3	1	4	1	12	2

earliest and most seriously affected, the paralysis being restricted to the inoculated limb in 9 cases, and spreading also to neighbouring muscles in 5 cases. Where neighbouring muscles were affected, in both upper and lower limbs, there was usually considerable return of function in them within three months, but not in the muscles first paralysed—namely, those of shoulder girdle and upper arm, or buttock and thigh. There was no particular grouping of the cases in time or in place—for example, in association with any particular clinic, instruments, or batch of prophylactic.

"The preponderance of upper limb paralysis in those immunized within two months suggests the influence of the inoculation in determining the site of paralysis, since inoculations in London are much more frequently done in the arm than in the leg. The only exception in this group was a child of 10 months who, 11 days after a first injection of diphtheria alum-precipitated toxoid in the left arm, developed poliomyelitis with paralysis of the left buttock and thigh. She has not been included among the 14 cases of 'related' inoculation and paralysis. (Two further cases of interest in this connexion were a child of 6 years who developed paralysis of the right shoulder girdle and upper arm 15 days after tonsillectomy in May, 1947, and a child of 4 years who developed paralysis of the left shoulder girdle and upper arm 15 days after tonsillectomy in October, 1949.) There was no reason to doubt the diagnosis of poliomyelitis in these cases, the stages of general symptoms, meningeal irritation, and paralysis, together with the spinal fluid findings, all being characteristic."

It is concluded that during periods of high or moderately high prevalence of poliomyelitis there is a definite but probably small risk that inoculation with the type of whooping cough and diphtheria prophylactic usually employed will be followed by serious flaccid paralysis of the inoculated limb in young children. "The paralysis particularly affects the muscles adjoining the site of inoculation."

Symposium Section

Khellin in Coronary Inadequacy

Khellin is the name of a crystalline substance derived from the seeds of the plant *Ammi visnaga*, which grows wild and abundantly in Arabia, Egypt and other Eastern Mediterranean countries. It is said to have been used for centuries for the treatment of conditions in which spasm of the smooth musculature is the dominant factor. The drug was studied pharmacologically in 1932 by Samaan,[1] and its chief physiologic effect was that it relaxed smooth muscle by direct action on the muscle fibers.

It was not until 1946 that Anrep, Barsoum, Kenawy and Misrahy[2] investigated its effect as a possible dilator of coronary arteries, although Kenawy and Barsoum[3] of this group had previously reported its use in the treatment of angina pectoris. They had treated 7 cases and thought the results were promising. Later with Anrep and Misrahy[2] they added 38 cases in which improvement was noted in 35. Following this Ayad[4] reported 83 per cent improvement in 23 cases. Anrep and associates[5] continued their investigations in Egypt and in 1949 contributed a clinical study which is the largest so far. Their study involved 250 cases of angina pectoris in which improvement was noted in 90 per cent. As a result of such encouraging results other studies have been inspired, and elsewhere in this issue will be found the two most recent reports[6] from America; others[7] during the current year were used in an earlier editorial comment.[8] So contributions from some of the leading cardiovascular clinics abroad and in this country make it possible to discuss what is thought of this new remedy for an important heart ailment.

The interest of the Egyptian workers in *Ammi visnaga* and its active principle, khellin, arose as a result of an accidental observation. For three years prior to their first report a member of their laboratory staff had been suffering from definite symptoms of coronary insufficiency. Anginal attacks were frequent. They were occurring not only after exertion but also spontaneously, especially after meals, and sometimes even at night. In addition to his coronary complaint, the man became a victim of renal colic of such severity that he had to stop his work. X-ray examination revealed the presence of three calculi in the left ureter. After taking various remedies without much benefit, he was advised to try a tincture of *Ammi visnaga*. This apparently was of some help as on the seventh day he "passed some sand and a calculus." At the time Anrep, Kenawy and Barsoum of the Physiological Laboratory of Fouad I University Hospital, Kasr-El-Aini, Cairo, Egypt, where these early observations were made, were not aware of his condition and their attention was drawn to him after his return to work. Previously he had behaved like a semi-invalid, but now appeared stronger and more vigorous; he moved faster, lost his apprehensive and frightened look, and could climb the staircase without the attacks of angina formerly induced by such effort. He attributed his improvement to the passage of the calculus, but

1. Samaan, K.: The Pharmacological Action of the Glucoside Khellin, *Quart. J. Pharm. & Pharmacol.*, **5**:6 and 183, 1932. Cited by 2 and others.
2. Anrep, G. V., Barsoum, G. S., Kenawy, M. R. and Misrahy, G.: *Ammi Visnaga* in Treatment of Anginal Syndrome. *Brit. Heart J.*, **8**:171 (October) 1946; Therapeutic Uses of Khellin; Method of Standardisation. *Lancet*, **1**:557 (April 26) 1947.
3. Kenawy, M. R. and Barsoum, G. S.: *Ammi Visnaga* in the Treatment of the Anginal Syndrome, *Gaz. Fac. Med.*, Cairo, **13**:39, 1945. Cited by 5 and others.
4. Ayad, H.: Khellin in Angina Pectoris, *Lancet*, **1**:305 (February 21) 1948.
5. Anrep, G. V., Kenawy, M. R. and Barsoum, G. S.: The Coronary Vasodilator Action of Khellin, *Am. Heart J.*, **37**:531 (April 1) 1949.
6. Armbrust, C. A., Jr. and Levine, S. A.: The Treatment of Angina Pectoris with a Preparation of Khellin (*Ammi Visnaga*), *Am. J. M. Sc.*, **220**: 127 (August) 1950; Best, M. M. and Coe, W. S.: Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests, *Circulation*, **2**:344 (September) 1950.

See pages 265 and 266.

7. Rosenman, R. H., Fishman, A. P., Kaplan, S. R., Levin, H. G. and Katz, L. N.: Observations on the Clinical Use of Visammin (Khellin), *J. A. M. A.*, **143**:160 (May 13) 1950; Dewar, H. A. and Grimson, T. A.: Khellin in the Treatment of Angina of Effort, *Brit. Heart J.*, **12**:54 (January) 1950.
8. Editorial: Khellin in Anginal Pain, *Internat. M. Digest*, **57**:184 (September 1950.

this proved to be wrong because a few days later his general condition became as bad as before. Anrep and his associates found, on investigation, that during the period of the renal colic the man consumed 20 cc. of tincture of *Ammi visnaga* per day. On the suspicion that visnaga was the cause of his temporary improvement, he was persuaded to repeat the treatment. The relief which followed was spectacular and he has continued to take the drug for over two years. So Anrep and his associates were inspired to begin their experimental and clinical observations which have led to the development of a new and promising remedy for an old and perplexing condition.

The plant *Ammi visnaga* is also known in Arabic as "Khella" so when the active principle was extracted from the seeds it was called Khellin. The local population in the Eastern Mediterranean countries, where it grows wild, have used decoctions of its seeds as a spasmodic since ancient times. In the Cairo study a preparation known as *Ammicardine* was supplied by the Alpha Laboratories of Cairo, Egypt. It is available in this country through Smith, Kline & French Laboratories as *Eskel* and as Khellin by Merck & Company. In the recent study by Armbrust and Levine[6] the preparation of Smith, Kline & French used is a mixture of approximately 75 per cent Khellin and visnagin (when assayed as khellin equivalent) 25 per cent.

Khellin was first prepared in an impure form by Mustapha in 1879, who also suggested the name, and again by Malosse in 1881, according to Armbrust and Levine. These recent writers, however, found that it was not until 1930 that Fantl and Salem isolated it in pure form, determined its composition, and suggested a structural formula which was somewhat modified by Spaeth and Gruber in 1938. Further study of these principles are under way and it is reasonable to expect that they will be improved and that some objectionable effects will be overcome.

The pharmacology of *Ammi visnaga,* Khella (as it is known in Arabic), and its derivatives khellin, visnagin and khellolglucoside are fully discussed in the article of Anrep and associates[5] and a complete bibliography is appended to their article for those who may be interested. So we will proceed to the clinical use of the drug.

Anrep and his associates tried out khellin in 300 patients suffering from coronary artery disease. The cases fell into two groups: (1) 250 patients with angina of effort or decubitus; (2) 50 patients with coronary thrombosis, with or without anginal attacks during the period of absolute recumbency. Khellin was used either as a continuous treatment to prevent or diminish the number of attacks or occasionally for the relief of actual attacks. The subjective effects of the drug were recorded in every case. Most of their patients were more or less stable and knew the amount of exercise which would evoke an attack. Most of them had been treated previously with other coronary vasodilator drugs such as aminophylline and theophylline. Objective tests were carried out on some of the patients by registration of the electrocardiographic changes caused by graded exercises before and after administration of khellin. Controlled exercise tolerance tests were made whenever the condition of the patient allowed. Patients giving a history of recent coronary thrombosis or showing any signs of myocardial failure were exempted from these tests. To eliminate any possible interference of a psychic nature in the action of the new drug, placebos were administered either in the form of injections or tablets containing no khellin, or without the patient being informed that the dose of khellin was suddenly reduced. No other drugs were given during the treatment except, when necessary, an occasional trinitrin tablet to some patients.

Anrep and associates administered the khellin in the following forms in their early study: (*a*) As a purified liquid extract containing 50 mg. of the active principle per cc. The dose given was 1 to 2 cc. diluted with water. This preparation has a bitter taste so its use was advocated with meals. (*b*) As tablets, each containing 50 mg. of khellin: 1 to 2 tablets were used after meals. (*c*) It was also used as an intramuscular injection in a strength of 50 mg. per cc.; 2 cc. were injected once or twice daily and during anginal attacks. It was found that the injection caused a slight local pain that lasted a few seconds.

In most of the cases of these early investigators, the tablets or liquid extract was used, but in severe cases a combined treatment of injections as well as oral

therapy was used. The minimal effective dose was calculated as 2 mg. per Kg. of body weight.

Early in 1950 Rosenman, Fishman, Kaplan, Levin and Katz[7] reported on 20 cases from the Cardiovascular Department of Michael Reese Hospital, Chicago. They used a preparation supplied by Smith, Kline & French, Philadelphia, who also sponsored their study. As mentioned, this preparation is known as Eskel. Recently the Smith, Kline & French Laboratories have developed more precise methods of assay which indicated that the 50 mg. tablets used in the Michael Reese study, as well as previous studies, contained only 40 mg. of active material and that 100 mg. ampuls contain only 70 mg. of active material. So Rosenman and associates explain this in a footnote in their article somewhat as an addendum to their discussion of dosage which was the same as that of Anrep's group in Cairo, Egypt. Armbrust and Levine[6] also used Eskel by mouth in the same doses. They gave these tablets containing 40 mg. of the active principle three times a day and likewise used placebos as did the two previous groups. They also evaluated their results, noting the amount of nitroglycerin tablets which patients used before as compared to after treatment.

Best and Coe of the Department of Medicine of the University of Louisville gave 50 mg. of khellin in tablets three times a day for a period of from two to four weeks. They likewise used placebos as a control and measured their results by the average number of 0.6 mg. nitroglycerin tablets required in a week. They too used exercise tolerance tests and took electrocardiograms before and after these tests. Anoxemia tests and the ergonovine test of Stein were also used.

The results obtained in the treatment of anginal symptoms of coronary insufficiency have been most impressive and encouraging. Anrep and associates, whose series is the largest, demonstrated that in 250 patients treated with khellin distinct improvement occurred in 140 cases, moderate improvement in 85 and no effect in 25. In many of their patients they found that clinical improvement was confirmed electrocardiographically. The drug was used also in 50 patients with recent coronary thrombosis with the object of improving the collateral circulation and relieving any associated anginal symptoms. Even though khellin is essentially an antispasmodic this objective seemed to have been attained. Rosenman and associates obtained good response in 11 of 14 patients, moderate improvement in 1 and no effect in 2. Then in 8 patients of pulmonary heart disease (cor pulmonale), distinct improvement in respiratory mechanics, color, exercise capacity and dyspnea followed the daily oral administration of 100 to 300 mg. of khellin daily. In addition, they found that single intramuscular injections of 200 mg. of khellin resulted in significant improvement in 9 of 21 patients with acute bronchial asthma. The response was prompt, occurring within 5 or 10 minutes, and often was dramatic but usually short-lived. Untoward reactions were observed in 17 cases. These were nausea, constipation, lightheadedness, dizziness, diarrhea, somnolence, insomnia, urticaria and dermatitis. The incidence of these reactions increased with larger doses. Nevertheless, they feel that the drug has therapeutic effects in angina pectoris, chronic pulmonary heart disease and, possibly, in acute bronchial asthma. Similar results were obtained by Armbrust and Levine and by Best and Coe whose impressions will be found in more detail in the abstracts of their articles elsewhere in this issue. Best and Coe noticed an increase in exercise tolerance and decrease in the number and severity of anginal attacks in 9 of their 14 patients. Moreover, they found that in 71.4 per cent, the electrocardiographic evidence of coronary insufficiency reverted to normal with khellin therapy.

Summarily, existing evidence indicates that this Egyptian drug is definitely beneficial in coronary disease and that it compares favorably with such generally used drugs as aminophylline. Its untoward effects, mainly nausea and vomiting, are still troublesome but all are hoping that further study more clearly to define its clinical usefulness, as expressed by Rosenman and associates, may overcome these effects. Certainly its source in the Eastern Mediterranean countries offers an unlimited supply for the production of the active principle. Consequently, with the superior laboratories in this country we should soon know more about it.

International Medical Digest

A Monthly Abstract Journal of Current Literature

Edited by Robert A. Strong, M. D.
with the collaboration of
Frederick Tice, M. D.
Irvine McQuarrie, M. D.
Maxwell M. Wintrobe, M. D.

Published by W. F. Prior Company, Inc.,
at Hagerstown, Maryland.

Vol. 57 NOVEMBER, 1950 No. 5

Irradiated Plasma-Borne Hepatitis

No small amount of relief was felt when evidence was brought forth that irradiation with ultraviolet ray seemed effective in destroying the icterogenic factor in human plasma which too frequently causes homologous serum hepatitis. It was welcomed as especially opportune at a time when plasma was again to be used to save the lives of those who were also again called upon to prevent the hordes of pusillanimous puppets of paranoiac punks from destroying the world. But three recently published reports[1, 2, 3] convey the disappointing information that in some instances what was believed to be an effective form of sterilization has failed and homologous serum hepatitis has been transmitted to recipients.

The first report, by Rosenthal, Bassen and Michael of the Second Medical Service and Hematology Division of the Laboratories of the Mount Sinai Hospital, concerned 3 patients who had been given irradiated plasma following bloodletting by venesection (phlebotomy) which it was hoped would reduce the blood volume in cases of polycythemia vera. During this study, 13 patients with polycythemia had phlebotomies followed by irradiated plasma. One unit was given in case 1 and 2 units in case 2. Oliphant and Hollaender, Wolf and associates, Blanchard, Stokes and associates and others had accumulated what seemed to be convincing evidence that the ultraviolet irradiation of plasma produced a protective effect on untreated plasma which prevented it from causing jaundice. The danger of untreated plasma was recognized at the outset of this study of 13 patients with polycythemia in whom phlebotomies and plasma were to be used with therapeutic hope. However, in this series in which irradiated plasma was used in case 1 and 2, jaundice appeared 120 and 106 days, respectively, following administration. In the third case, jaundice developed 71 days after transfusion from a donor who had received irradiated plasma. Rosenthal and his associates maintain that their object was only to present the facts as they occurred and they suggest the possibility that these cases may have been spontaneous. This was in the realm of possibility but they believe that the evidence they obtained indicates strongly that the treated plasma was responsible.

This impression seems fully sustained by the second report, by Barnett, Fox and Snavely, of 3 cases of severe hepatitis, 2 of them fatal, following the administration of commercially irradiated human plasma.

Moreover, James, Korns and Wright (Albany) reported an outbreak of apparent homologous serum jaundice in 10 of 20 patients who had received irradiated human plasma from a single commercial lot. At the time their report was submitted for publication they had no knowledge of two other instances which had occurred in New York City and Stamford, Connecticut. Later, in following up their cases, they found that two others had developed jaundice and they still had others to contact.

These three reports are conveniently available to our readers in the *J.A.M.A.* and should be read for further details. Barnett and associates suggest several possible reasons for the discrepancy between experimental results of Blanchard and his group and the occurrence of hepatitis following the use of commercially irradiated plasma: (1) Large scale irradiation and subsequent storage may not simulate the smaller scale experiments. (2) The amount

1. Rosenthal, N., Bassen, F. A. and Michael, S. R.: Probable Transmission of Viral Hepatitis by Ultraviolet-Irradiated Plasma, *J. A. M. A.*, **144:** 224 (September 16) 1950.
2. Barnett, R. N., Fox, R. A. and Snavely, J. G.: Hepatitis Following the Use of Irradiated Human Plasma, *J. A. M. A.*, **144:** 226 (September 16) 1950.
3. James, G., Korns, R. F. and Wright, A. W.: Homologous Serum Jaundice Associated with Use of Irradiated Plasma, *J. A. M. A.*, **144:** 228 (September 16) 1950.

of plasma commonly used in practice (250 or more) is far larger than that used in the experiments (7 cc.). (3) Irradiation may be ineffectual and the experimental results may have occurred by chance. (4) There may be several strains of virus not equally affected by ultraviolet irradiation. To this we may add, and even hope, that some technical error in the irradiation may have been the cause.

Let us hope that further studies will reveal the answers to the questions which these convincing reports have raised.

Congenital Malaria

The possibility of infants acquiring malaria in utero has again been brought up by B. S. Jones[1] of the British Colonial Service in a recent article. He contends that a considerable divergence of opinion persists regarding the frequency with which it occurs but that there can be no doubt that it does. This is in accord with what we have encountered and have discussed repeatedly over many years. The latest[2] of these discussions was in 1946.

Back in the years when malaria was more prevalent in the Southern states than it is now, it was a matter of common knowledge that infants acquired the parasites early in life. This knowledge was equally common in other parts of the world where malaria is endemic. Col. Charles F. Craig, M.C., U.S.A., D.S.M. (ret.), whose contributions to every phase of tropical medicine in general, and malaria in particular, have made him an international authority and whose writings have been consulted by all seeking authentic information, discovered early in his career in the Philippine Islands that children from 1 to 5 years of age showed latent malaria in 75 per cent of those examined, 5 to 10 years, 37 per cent and 10 to 15 years, 27 per cent. Manson-Bahr cites that Blacklock and Gordon discovered, in Sierra Leone, that in pregnant women infected with *Plasmodium falciparum*, 36 per cent sustain intensive infection in the placenta leading to death of the fetus. Jean and van Nitsen record 8 children, either born dead or dying soon after birth, in whom they showed malarial schizonts in the spleen. Wickramasuriya, in Ceylon, found that congenital malaria is a definite clinical entity, and in 3 out of 6 proved cases of transplacental infections, the death of the fetus could be attributed to malaria contracted in utero.

The opinion has been frequently expressed that a physiologically healthy placenta will not permit the passage of parasites from the mother to the fetus. Manson-Bahr and others contend that the mechanism has been assumed to be that the parasites pass from the maternal circulation to that of the fetus as the result of mechanical damage to the placenta or of pathologic changes in it induced by malarial infection.

Long ago Colonel Craig contended that congenital malaria can and does occur, but that it is rare and may be considered of very little practical importance.

It still seems to interest malariologists, however, especially those writing in British journals. Jones in his recent communication, which reopened the question, puts forward evidence to support the view that while congenital malaria is very rare among natives of hyperendemic areas, it is common among nonimmune subjects entering such areas from malaria-free countries. One suggestion concerning this is that the placenta of nonimmune mothers undergoes changes which render it more friable and permeable. This is believed to be due to the malarial infection which they acquire while pregnant. In the cases which Jones records, however, only 1 of 3 mothers admitted any recent malarial attack. His 3 cases of congenital malaria, as diagnosed by the finding of tertian rings in the cord blood of the infants, he believed, justified his conclusion that among European women of relatively low immunity congenital transmission of malaria is by no means rare when they are infected with the Lagos (Africa) strain of *P. falciparum*. His 3 cases of congenital malaria were found among 37 infants born of European women in February, 1949, at a hospital in Lagos.

This seems definitely to establish again that there is such a clinical entity as congenital malaria, although Colonel Craig's contention that it is rare does not seem to be refuted.

1. Jones, B. S.: Congenital Malaria, *Brit. M. J.*, **2**:439 (August 19) 1950.
2. Editorial: Congenital Malaria, *Internat. M. Digest*, **48**:373 (June) 1946.